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Interventions for prevention of herpes simplex labialis (cold sores on the lips) (Review)

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[Intervention Review]

Interventions for prevention of herpes simplex labialis (cold sores on the lips)

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ABSTRACT

Background

Herpes simplex labialis (HSL), also known as cold sores, is a common disease of the lips caused by the herpes simplex virus, which is found throughout the world. It presents as a painful vesicular eruption, forming unsightly crusts, which cause cosmetic disfigurement and psychosocial distress. There is no cure available, and it recurs periodically.

Objectives

To assess the effects of interventions for the prevention of HSL in people of all ages.

Search methods

We searched the following databases up to 19 May 2015: the Cochrane Skin Group Specialised Register, the Oral Health Group Specialised Register, CENTRAL in the Cochrane Library (Issue 4, 2015), MEDLINE (from 1946), EMBASE (from 1974), LILACS (from 1982), the China National Knowledge Infrastructure (CNKI) database, Airiti Library, and 5 trial registers. To identify further references to relevant randomised controlled trials, we scanned the bibliographies of included studies and published reviews, and we also contacted the original researchers of our included studies.

Selection criteria

Randomised controlled trials (RCTs) of interventions for preventing HSL in immunocompetent people.

Data collection and analysis

Two authors independently selected trials, extracted data, and assessed the risk of bias. A third author was available for resolving differences of opinion.

Main results

This review included 32 RCTs, with a total of 2640 immunocompetent participants, covering 19 treatments. The quality of the body of evidence was low to moderate for most outcomes, but was very low for a few outcomes. Our primary outcomes were 'Incidence of HSL' and 'Adverse effects during use of the preventative intervention'.

The evidence for short-term (≤ 1 month) use of oral aciclovir in preventing recurrent HSL was inconsistent across the doses used in the studies: 2 RCTs showed low quality evidence for a reduced recurrence of HSL with aciclovir 400 mg twice daily (risk ratio (RR) 0.26, 95% confidence interval (CI) 0.13 to 0.51; n = 177), while 1 RCT testing aciclovir 800 mg twice daily and 2 RCTs testing 200 mg 5 times daily found no similar preventive effects (RR 1.08, 95% CI 0.62 to 1.87; n = 237; moderate quality evidence and RR 0.46, 95% CI 0.20 to 1.07; n = 66; low quality evidence, respectively). The direction of intervention effect was unrelated to the risk of bias. The evidence from 1 RCT for the effect of short-term use of valaciclovir in reducing recurrence of HSL by clinical evaluation was uncertain (RR 0.55, 95% CI 0.23 to 1.28; n = 125; moderate quality evidence), as was the evidence from 1 RCT testing short-term use of famciclovir.

Long-term (> 1 month) use of oral antiviral agents reduced the recurrence of HSL. There was low quality evidence from 1 RCT that long-term use of oral aciclovir reduced clinical recurrences (1.80 versus 0.85 episodes per participant per a 4-month period, P = 0.009) and virological recurrence (1.40 versus 0.40 episodes per participant per a 4-month period, P = 0.003). One RCT found long-term use of valaciclovir effective in reducing the incidence of HSL (with a decrease of 0.09 episodes per participant per month; n = 95). One RCT found that a long-term suppressive regimen of valaciclovir had a lower incidence of HSL than an episodic regimen of valciclovir (difference in means (MD) -0.10 episodes per participant per month, 95% CI -0.16 to -0.05; n = 120).

These trials found no increase in adverse events associated with the use of oral antiviral agents (moderate quality evidence).

There was no evidence to show that short-term use of topical antiviral agents prevented recurrent HSL. There was moderate quality evidence from 2 RCTs that topical aciclovir 5% cream probably has little effect on preventing recurrence of HSL (pooled RR 0.91, 95% CI 0.48 to 1.72; n = 271). There was moderate quality evidence from a single RCT that topical foscarnet 3% cream has little effect in preventing HSL (RR 1.08, 95% CI 0.82 to 1.40; n = 295).

The efficacy of long-term use of topical aciclovir cream was uncertain. One RCT found significantly fewer research-diagnosed recurrences of HSL when on aciclovir cream treatment than on placebo (P < 0.05), but found no significant differences in the mean number of participant-reported recurrences between the 2 groups (P ≥ 0.05). One RCT found no preventive effect of topical application of 1,5-pentanediol gel for 26 weeks (P > 0.05). Another RCT found that the group who used 2-hydroxypropyl-β-cyclo dextrin 20% gel for 6 months had significantly more recurrences than the placebo group (P = 0.003).

These studies found no increase in adverse events related to the use of topical antiviral agents.

Two RCTs found that the application of sunscreen significantly prevented recurrent HSL induced by experimental ultraviolet light (pooled RR 0.07, 95% CI 0.01 to 0.33; n = 111), but another RCT found that sunscreen did not prevent HSL induced by sunlight (RR 1.13, 95% CI 0.25 to 5.06; n = 51). These RCTs did not report adverse events.

There were very few data suggesting that thymopentin, low-level laser therapy, and hypnotherapy are effective in preventing recurrent HSL, with one to two RCTs for each intervention. We failed to find any evidence of efficacy for lysine, LongoVital® supplementation, gamma globulin, herpes simplex virus (HSV) type I subunit vaccine, and yellow fever vaccine in preventing HSL. There were no consistent data supporting the efficacy of levamisole and interferon, which were also associated with an increased risk of adverse effects such as fever.

Authors' conclusions

The current evidence demonstrates that long-term use of oral antiviral agents can prevent HSL, but the clinical benefit is small. We did not find evidence of an increased risk of adverse events. On the other hand, the evidence on topical antiviral agents and other interventions either showed no efficacy or could not confirm their efficacy in preventing HSL.

PLAIN LANGUAGE SUMMARY

Measures for preventing cold sores

Review question

What measures are effective in preventing recurrence of cold sores?

Background

A cold sore is an irritating recurrent viral infection with no proven cure. It gives rise to painful vesicles on the lips that form unsightly crusts, causing an unpleasant look and mental distress. We aimed to examine the effects of available measures for preventing recurrence of cold sores in people with normal immunity.

Study characteristics

We examined the research published up to 19 May 2015. We wanted to include studies only if receiving one preventative measure or another was decided by chance. This research method, termed randomised controlled trial (RCT), is the best way to test that a preventive effect is caused by the measure being tested. We found 32 RCTs that included 2640 people and examined 19 preventative measures. The drug manufacturer funded a total of 18 out of 32 studies, non-profit organisations funded 4, and we do not know how the other 10 were funded.

Key results

Long-term use of antiviral drugs taken by mouth prevented cold sores, though with a very small decrease of 0.09 episodes per person per month. The preventative effect of long-term use of aciclovir cream applied to the lips was uncertain. Long-term use of 1,5-pentanediol gel and 2-hydroxypropyl-β-cyclo dextrin 20% gel applied to the lips did not prevent cold sores.

Short-term use of either antiviral drugs or creams did not prevent cold sores. Neither short-term nor long-term use of these antiviral drugs or creams appeared to cause side-effects.

The preventative effects of sunscreen were uncertain. Application of sunscreen prevented cold sores induced by experimental ultraviolet light, but did not prevent cold sores induced by sunlight.

We found very little evidence about the preventative effects of thymopentin, low-energy laser, and hypnotherapy for cold sores. The available evidence found no preventative effects of lysine, LongoVital® supplementation, gamma globulin, herpes virus vaccine, and yellow fever vaccine. There were no consistent data to confirm that levamisole and interferon do prevent cold sores.

These studies found no increase in adverse events related to the use of topical antiviral agents.

Quality of the evidence

The quality of the evidence was low to moderate for most outcomes, but was very low for some outcomes.

Summary of findings for the main comparison. Oral aciclovir (short-term) compared with placebo for prevention of herpes simplex labialis

Oral aciclovir (short-term) compared with placebo for prevention of herpes simplex labialis

Patient or population: participants with recurrent herpes simplex labialis (cold sores on the lips)
Settings: ski sites and university hospitals
Intervention: oral aciclovir (short-term)
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Oral aciclovir (short-term)				
Incidence of herpes labialis during use of the preventative intervention (by clinical evaluation) - aciclovir 800 mg twice daily	**Study population**		**RR 1.08** (0.62 to 1.87)	237 (1 study)	⊕⊕⊕⊖ **Moderate**[1]	-
	171 per 1000	**184 per 1000** (106 to 319)				
	Moderate					
	171 per 1000	**185 per 1000** (106 to 320)				
Incidence of herpes labialis during use of the preventative intervention (by clinical evaluation) - aciclovir 400 mg twice daily	**Study population**		**RR 0.26** (0.13 to 0.51)	177 (2 studies)	⊕⊕⊖⊖ **Low**[2]	-
	364 per 1000	**95 per 1000** (47 to 185)				
	Moderate					
	538 per 1000	**140 per 1000** (70 to 274)				
Incidence of herpes labialis during use of the preventative intervention (by clinical evaluation) - aciclovir 200 mg 5 times/day	**Study population**		**RR 0.46** (0.2 to 1.07)	66 (1 study)	⊕⊕⊖⊖ **Low**[3]	-
	394 per 1000	**181 per 1000** (79 to 422)				
	Moderate					

	394 per 1000	**181 per 1000** (79 to 422)				
Incidence of herpes labialis during use of the preventative intervention (by culture) - aciclovir 400 mg twice daily	**Study population**		**RR 0.05** (0 to 0.7)	30 (1 study)	⊕⊕⊝⊝ **Low**[3]	-
	750 per 1000	**38 per 1000** (0 to 525)				
	Moderate					
	750 per 1000	**38 per 1000** (0 to 525)				
Adverse effects during use of the preventative intervention - aciclovir 800 mg twice daily	**Study population**		**RR 0.98** (0.7 to 1.38)	239 (1 study)	⊕⊕⊕⊝ **Moderate**[1]	-
	363 per 1000	**356 per 1000** (254 to 501)				
	Moderate					
	363 per 1000	**356 per 1000** (254 to 501)				
Adverse effects during use of the preventative intervention - aciclovir 400 mg twice daily	**Study population**		**RR 2.3** (0.62 to 8.58)	183 (2 studies)	⊕⊕⊝⊝ **Low**[2]	-
	33 per 1000	**75 per 1000** (20 to 280)				
	Moderate					
	20 per 1000	**46 per 1000** (12 to 172)				

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **GRADE:** Grading of Recommendations Assessment, Development and Evaluation; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level due to imprecision: the available evidence is limited to one single randomised trial.

[2]Downgraded two levels due to risk of bias and imprecision: the available evidence is limited to two randomised trials, with one having a high risk of other biases.
[3]Downgraded two levels due to risk of bias and imprecision: the available evidence is limited to one single randomised trial with a high risk of reporting bias.

Summary of findings 2. Oral aciclovir (long-term) compared with placebo for prevention of herpes simplex labialis

Oral aciclovir (long-term) compared with placebo for prevention of herpes simplex labialis

Patient or population: participants with recurrent herpes simplex labialis
Settings: a medical centre
Intervention: oral aciclovir (long-term)
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	placebo	Oral aciclovir (long-term)				
Incidence of herpes labialis during use of the preventative intervention (by culture)	1.40 episodes per participant per a 4-month period	0.40 episodes per participant per a 4-month period	Not estimable	40 (1 study)	⊕⊕⊖⊖ **Low**[1]	-
Incidence of herpes labialis during use of the preventative intervention (by clinical evaluation)	1.80 episodes per participant per a 4-month period	0.85 episodes per participant per a 4-month period	Not estimable	40 (1 study)	⊕⊕⊖⊖ **Low**[1]	-
Duration of attack of herpes labialis during use of the preventative intervention	-	The mean duration of attack of herpes labialis during use of the preventative intervention in the intervention groups was **3.6 lower** (7.2 lower to 0 higher)	-	40 (1 study)	⊕⊕⊖⊖ **Low**[1]	-
Rate of adherence to the regimen of the preventative intervention	99% of the prescribed study medication	99% of the prescribed study medication	-	40 (1 study)	⊕⊕⊖⊖ **Low**[1]	-

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **GRADE:** Grading of Recommendations Assessment, Development and Evaluation; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded two levels due to risk of bias and imprecision: the available evidence is limited to one single randomised trial with a high risk of reporting bias.

Summary of findings 3. Valaciclovir (short-term) compared with placebo for prevention of herpes simplex labialis

Valaciclovir (short-term) compared with placebo for prevention of herpes simplex labialis

Patient or population: participants with recurrent herpes simplex labialis
Settings: a university hospital
Intervention: valaciclovir (short-term)
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Valaciclovir (short-term)				
Incidence of HSL during use of the preventative intervention (by clinical evaluation)	**Study population**		**RR 0.55** (0.23 to 1.28)	125 (1 study)	⊕⊕⊕⊖ **Moderate**[1]	-
	206 per 1000	**113 per 1000** (47 to 264)				
	Moderate					
	206 per 1000	**113 per 1000** (47 to 264)				
Incidence of HSL during use of the preventative intervention (by culture)	**Study population**		**RR 0.47** (0.21 to 1.08)	125 (1 study)	⊕⊕⊕⊖ **Moderate**[1]	-
	238 per 1000	**112 per 1000** (50 to 257)				
	Moderate					
	238 per 1000	**112 per 1000**				

		(50 to 257)				
Adverse effects during use of the preventative intervention	**Study population**		**RR 1.33** (0.71 to 2.5)	125 (1 study)	⊕⊕⊕⊖ **Moderate**[1]	-
	206 per 1000	**274 per 1000** (147 to 516)				
	Moderate					
	206 per 1000	**274 per 1000** (146 to 515)				
Viral load (shedding) in saliva	**Study population**		**RR 0.16** (0.02 to 1.26)	120 (1 study)	⊕⊕⊕⊖ **Moderate**[1]	-
	103 per 1000	**17 per 1000** (2 to 130)				
	Moderate					
	103 per 1000	**16 per 1000** (2 to 130)				

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **GRADE:** Grading of Recommendations Assessment, Development and Evaluation; **HSL:** herpes simplex labialis; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level due to imprecision: the available evidence is limited to one single randomised trial.

Summary of findings 4. Valaciclovir (long-term) compared with placebo for prevention of herpes labialis

Valaciclovir (long-term) compared with placebo for prevention of herpes labialis

Patient or population: participants with recurrent herpes labialis
Settings: a university hospital
Intervention: valaciclovir (long-term)
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Valaciclovir (long-term)				
Incidence of herpes labialis during use of the preventative intervention	0.21 episodes per participant per month	0.12 episodes per participant per month	Not estimable	95 (1 study)	⊕⊕⊕⊖ **Moderate**[1]	-
Adverse effects during use of the preventative intervention	**Study population**		**RR 0.86** (0.51 to 1.46)	95 (1 study)	⊕⊕⊕⊖ **Moderate**[1]	-
	396 per 1000	**340 per 1000** (202 to 578)				
	Moderate					
	396 per 1000	**341 per 1000** (202 to 578)				

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **GRADE:** Grading of Recommendations Assessment, Development and Evaluation; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level due to imprecision: the available evidence is limited to one single randomised trial.

Summary of findings 5. Valaciclovir (suppressive regimen compared with episodic regimen) for prevention of herpes labialis

Valaciclovir (suppressive regimen compared with episodic regimen) for prevention of herpes labialis

Patient or population: participants with recurrent herpes labialis
Settings: a university hospital
Intervention: suppressive regimen
Comparison: episodic regimen

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Episodic regimen	Suppressive regimen				
Incidence of herpes labialis during use of the preventative intervention (number of recurrences per participant per month)	0.1775 ± 0.1975	0.075 ± 0.1025	The mean incidence of herpes labialis during use of the preventative intervention in the intervention groups was **0.1 lower** (0.16 to 0.05 lower)	120 (1 study)	⊕⊖⊖⊖ **Very low**[1]	-
Adverse effects during use of the preventative intervention	**Study population**		**RR 1.21** (0.78 to 1.87)	152 (1 study)	⊕⊖⊖⊖ **Very low**[1]	-
	316 per 1000	**382 per 1000** (246 to 591)				
	Moderate					
	316 per 1000	**382 per 1000** (246 to 591)				
Duration of attack of recurrent herpes labialis during use of the preventative intervention	2.86 ± 3.10 days	1.78 ± 2.92 days	The mean duration of attack of recurrent herpes labialis during use of the preventative intervention in the intervention groups was **1.08 days shorter** (2.16 lower to 0 higher)	120 (1 study)	⊕⊖⊖⊖ **Very low**[1]	-
Severity (pain) of attack of recurrent herpes labialis during use of the preventative intervention	0.23 ± 0.32	0.14 ± 0.27	The mean severity (pain) of attack of recurrent herpes labialis during use of the preventative intervention in the intervention groups was **0.09 lower** (0.2 lower to 0.02 higher)	120 (1 study)	⊕⊖⊖⊖ **Very low**[1]	-
Severity (maximum total lesion area) of attack of recurrent herpes labialis during use of the preventative intervention	10.52 ± 19.45 mm^2	5.14 ± 9.98 mm^2	The mean severity (maximum total lesion area) of attack of recurrent herpes labialis during use of the preventative intervention in the in-	120 (1 study)	⊕⊖⊖⊖ **Very low**[1]	-

		tervention groups was **5.38 smaller** (10.91 lower to 0.15 higher)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **GRADE:** Grading of Recommendations Assessment, Development and Evaluation; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded three levels due to imprecision and multiple risk of biases in performance, detection, attrition, and other sources: the available evidence is limited to one single randomised trial with a high risk of biases.

Summary of findings 6. Famciclovir compared with placebo for prevention of herpes labialis

Famciclovir compared with placebo for prevention of herpes labialis

Patient or population: participants with recurrent herpes labialis
Settings: multicentre
Intervention: famciclovir
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Famciclovir				
Incidence of herpes labialis during use of the preventative intervention (by clinical evaluation) - famciclovir 125 mg	**Study population**		**RR 0.74** (0.5 to 1.11)	120 (1 study)	⊕⊕⊕⊖ **Moderate**[1]	-
	517 per 1000	**382 per 1000** (258 to 574)				
	Moderate					
	517 per 1000	**383 per 1000** (259 to 574)				
	Study population		**RR 0.69** (0.45 to 1.04)	122 (1 study)	⊕⊕⊕⊖ **Moderate**[1]	-

Incidence of herpes labialis during use of the preventative intervention (by clinical evaluation) - famciclovir 250 mg	**517 per 1000**	**357 per 1000** (232 to 537)				
	Moderate					
	517 per 1000	**357 per 1000** (233 to 538)				
Incidence of herpes labialis during use of the preventative intervention (by clinical evaluation) - famciclovir 500 mg	**Study population**		**RR 0.82** (0.56 to 1.21)	121 (1 study)	⊕⊕⊕⊖ **Moderate**[1]	-
	517 per 1000	**424 per 1000** (289 to 625)				
	Moderate					
	517 per 1000	**424 per 1000** (290 to 626)				
Duration of attack of recurrent herpes labialis during use of the preventative intervention - famciclovir 125 mg	**Study population**		**HR 1.63** (0.84 to 3.15)	47 (1 study)	⊕⊕⊕⊖ **Moderate**[1]	-
	See comment[2]	See comment[2]				
Duration of attack of recurrent herpes labialis during use of the preventative intervention - famciclovir 250 mg	**Study population**		**HR 1.59** (0.79 to 3.2)	45 (1 study)	⊕⊕⊕⊖ **Moderate**[1]	-
	See comment[2]	See comment[2]				
Duration of attack of recurrent herpes labialis during use of the preventative intervention - famciclovir 500 mg	**Study population**		**HR 2.39** (1.23 to 4.63)	51 (1 study)	⊕⊕⊕⊖ **Moderate**[1]	-
	See comment[2]	Shortened by 2.8 days				

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **GRADE:** Grading of Recommendations Assessment, Development and Evaluation; **HR:** hazard ratio; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level due to imprecision: the available evidence is limited to one single randomised trial.
[2]Data unavailable.

Summary of findings 7. Levamisole compared with placebo for prevention of herpes labialis

Levamisole compared with placebo for prevention of herpes labialis

Patient or population: participants with recurrent herpes labialis
Settings: a university hospital
Intervention: levamisole
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Levamisole				
Incidence of herpes labialis during use of the preventative intervention	2.7 ± 2.3 recurrences during a 6-month period	The mean incidence of herpes labialis during use of the preventative intervention in the intervention groups was **2 lower** (2.24 to 1.76 lower) during a 6-month period	-	72 (1 study)	⊕⊖⊖⊖ **Very low**[1]	Of the 99 participants randomised, 27 (27.2%) did not complete the trial and were excluded from the analysis, with 19 (39.6%) in the levamisole group and 8 (15.7%) in the placebo group
Adverse effects during use of the preventative intervention (leading to withdrawal)	**Study population**		See comment	99 (1 study)	⊕⊖⊖⊖ **Very low**[1]	Risks were calculated from pooled risk differences
	157 per 1000	**395 per 1000** (227 to 566)				
	Moderate					
	157 per 1000	**396 per 1000** (228 to 567)				
Duration of attack of recurrent herpes labialis during use of the preventative intervention	8.2 ± 2.8 days	The mean duration of attack of recurrent herpes labialis during use of the preventative intervention in the intervention groups was **0.7 days longer** (0.22 to 1.18 longer)	-	72 (1 study)	⊕⊖⊖⊖ **Very low**[1]	-

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **GRADE:** Grading of Recommendations Assessment, Development and Evaluation.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded three levels due to imprecision and attrition and other biases: the available evidence is limited to a single study with a high risk of attrition and other biases.

Summary of findings 8. Lysine compared with placebo for prevention of herpes labialis

Lysine compared with placebo for prevention of herpes labialis

Patient or population: participants with recurrent herpes simplex labialis (cold sores on the lips)
Settings: a university hospital
Intervention: lysine
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Lysine				
Incidence of herpes labialis during use of the preventative intervention (number of recurrences per participant per month)	-	The mean incidence of herpes labialis during use of the preventative intervention in the intervention groups was **0.04 lower** (0.37 lower to 0.29 higher)	-	26 (1 study)	⊕⊖⊖⊖ **Very low**[1]	-

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **GRADE:** Grading of Recommendations Assessment, Development and Evaluation.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded three levels due to imprecision and reporting and other biases: the available evidence is limited to a single study with a high risk of reporting and other biases.

Summary of findings 9. Topical aciclovir (short-term) compared with placebo for prevention of herpes labialis

Topical aciclovir (short-term) compared with placebo for prevention of herpes labialis

Patient or population: participants with recurrent herpes labialis
Settings: ski sites and university hospitals
Intervention: topical aciclovir (short-term)
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Topical aciclovir (short-term)				
Incidence of herpes labialis during use of the preventative intervention	**Study population**		**RR 0.91** (0.48 to 1.72)	271 (2 studies)	⊕⊕⊕⊖ **Moderate**[1]	-
	304 per 1000	**276 per 1000** (146 to 522)				
	Moderate					
	328 per 1000	**298 per 1000** (157 to 564)				
Adverse effects during use of the preventative intervention	**Study population**		**RR 1.17** (0.59 to 2.32)	191 (1 study)	⊕⊕⊖⊖ **Low**[2]	-
	135 per 1000	**158 per 1000** (80 to 314)				
	Moderate					
	135 per 1000	**158 per 1000** (80 to 313)				
Severity (aborted lesions) of attack of recurrent herpes labialis during use of the preventative intervention	**Study population**		**RR 1.02** (0.19 to 5.57)	52 (1 study)	⊕⊕⊖⊖ **Low**[2]	-
	95 per 1000	**97 per 1000** (18 to 530)				
	Moderate					
	95 per 1000	**97 per 1000**				

		(18 to 529)				
Incidence of herpes labialis after use of the preventative intervention	**Study population**		**RR 0.35** (0.13 to 0.94)	181 (1 study)	⊕⊕⊖⊖ **Low**[2]	-
	156 per 1000	**54 per 1000** (20 to 146)				
	Moderate					
	156 per 1000	**55 per 1000** (20 to 147)				

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **GRADE:** Grading of Recommendations Assessment, Development and Evaluation; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level due to risk of bias: the evidence is from two trials with a high risk of reporting bias.
[2]Downgraded two levels due to risk of bias and imprecision: the evidence is from a single trial with a high risk of bias.

Summary of findings 10. Topical aciclovir and 348U87 cream (short-term) compared with placebo for prevention of herpes labialis

Topical aciclovir and 348U87 cream (short-term) compared with placebo for prevention of herpes labialis

Patient or population: participants with recurrent herpes labialis
Settings: research institutes
Intervention: topical aciclovir and 348U87 cream (short-term)
Comparison: placebo

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**Number of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Placebo	**Topical aciclovir and 348U87 cream (short-term)**				
Incidence of herpes labialis during use of the preventative intervention (by culture)	**Study population**		**RR 0.78** (0.19 to 3.14)	51 (1 study)	⊕⊖⊖⊖ **Very low**[1]	-

	154 per 1000	**120 per 1000** (29 to 483)				
	Moderate					
	154 per 1000	**120 per 1000** (29 to 484)				
Incidence of herpes labialis during use of the preventative intervention (by clinical evaluation)	**Study population**		**RR 1.46** (0.53 to 3.99)	51 (1 study)	⊕⊖⊖⊖ **Very low**[1]	-
	192 per 1000	**281 per 1000** (102 to 767)				
	Moderate					
	192 per 1000	**280 per 1000** (102 to 766)				
Duration of attack of recurrent herpes labialis during use of the preventative intervention	-	The mean duration of attack of recurrent herpes labialis during use of the preventative intervention in the intervention groups was **2.5 days longer** (1.39 shorter to 6.39 longer)	-	9 (1 study)	⊕⊖⊖⊖ **Very low**[1]	-
Severity of attack of recurrent herpes labialis during use of the preventative intervention (maximum lesion area)	-	The mean severity of attack of recurrent herpes labialis during use of the preventative intervention (maximum lesion area) in the intervention groups was **73 larger** (42.22 smaller to 188.22 larger)	-	9 (1 study)	⊕⊖⊖⊖ **Very low**[1]	-

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **GRADE:** Grading of Recommendations Assessment, Development and Evaluation; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded three levels due to imprecision and reporting and other biases: the available evidence is from a single trial with a high risk of reporting and other biases.

Summary of findings 11. Topical foscarnet compared with placebo for prevention of herpes labialis

Topical foscarnet compared with placebo for prevention of herpes labialis

Patient or population: participants with recurrent herpes labialis
Settings: medical centres
Intervention: topical foscarnet
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Topical foscarnet				
Incidence of herpes labialis during use of the preventative intervention	**Study population**		**RR 1.08** (0.82 to 1.4)	295 (1 study)	⊕⊕⊕⊖ **Moderate**[1]	-
	408 per 1000	**441 per 1000** (335 to 571)				
	Moderate					
	408 per 1000	**441 per 1000** (335 to 571)				
Adverse effects during use of the preventative intervention (leading to discontinuation)	**Study population**		**RR 2.96** (0.12 to 72.11)	302 (1 study)	⊕⊕⊕⊖ **Moderate**[1]	-
	0 per 1000	**0 per 1000** (0 to 0)				
	Moderate					
	0 per 1000	**0 per 1000** (0 to 0)				
Adverse effects during use of the preventative intervention (application site reactions)	**Study population**		**RR 2.47** (0.79 to 7.69)	302 (1 study)	⊕⊕⊕⊖ **Moderate**[1]	-
	27 per 1000	**66 per 1000** (21 to 205)				
	Moderate					
	27 per 1000	**67 per 1000**				

		(21 to 208)				
Duration of attack of recurrent herpes labialis during use of the preventative intervention (healing time)	-	The mean duration of attack of recurrent herpes labialis during use of the preventative intervention (healing time) in the intervention groups was **0.21 days shorter** (1.68 shorter to 1.26 longer)	-	125 (1 study)	⊕⊕⊕⊖ **Moderate**[1]	-
Severity of attack of recurrent herpes labialis during use of the preventative intervention (mean lesion area)	-	The mean severity of attack of recurrent herpes labialis during use of the preventative intervention (mean lesion area) in the intervention groups was **16 lower** (38.96 lower to 6.96 higher)	-	124 (1 study)	⊕⊕⊕⊖ **Moderate**[1]	-
Severity of attack of recurrent herpes labialis during use of the preventative intervention (maximum lesion area)	-	The mean severity of attack of recurrent herpes labialis during use of the preventative intervention (maximum lesion area) in the intervention groups was **30 lower** (72.64 lower to 12.64 higher)	-	124 (1 study)	⊕⊕⊕⊖ **Moderate**[1]	-
Severity of attack of recurrent herpes labialis during use of the preventative intervention (duration of pain)	-	The mean severity of attack of recurrent herpes labialis during use of the preventative intervention (duration of pain) in the intervention groups was **0.1 higher** (1.11 lower to 1.31 higher)	-	113 (1 study)	⊕⊕⊕⊖ **Moderate**[1]	-

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **GRADE:** Grading of Recommendations Assessment, Development and Evaluation; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level due to imprecision: the available evidence is from a single trial.

Summary of findings 12. Topical 1,5-pentanediol compared with placebo for prevention of herpes labialis

Topical 1,5-pentanediol compared with placebo for prevention of herpes labialis

Patient or population: participants with recurrent herpes labialis
Settings: study centres
Intervention: topical 1,5-pentanediol
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Topical 1,5-pentanediol				
Incidence of herpes labialis during use of the preventative intervention	**Study population**		Not estimable	102 (1 study)	⊕⊕⊕⊖ **Moderate**[1]	P > 0.05 calculated using the Mann-Whitney test by the trialists
	109 episodes out of 50	**120 episodes out of 52**				
	Moderate					
	-	-				
Adverse effects during use of the preventative intervention	**Study population**		Not estimable	102 (1 study)	⊕⊕⊕⊖ **Moderate**[1]	-
	See comment	See comment				
	Moderate					
	-	-				
Severity (blistering, swelling, or pain) of recurrence	**Study population**		**RR 1.05** (0.91 to 1.2)	224 (1 study)	⊕⊕⊕⊖ **Moderate**[1]	-
	756 per 1000	**794 per 1000** (688 to 908)				
	Moderate					
	756 per 1000	**794 per 1000** (688 to 907)				

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **GRADE:** Grading of Recommendations Assessment, Development and Evaluation; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level due to imprecision: the available evidence is from a single study.

Summary of findings 13. Sunscreen compared with placebo for prevention of herpes labialis

Sunscreen compared with placebo for prevention of herpes labialis

Patient or population: participants with recurrent herpes labialis
Settings: single centre and multicentre
Intervention: sunscreen
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Sunscreen				
Incidence of herpes labialis during use of the preventative intervention (by clinical evaluation) - solar radiation	**Study population**		**RR 1.12** (0.25 to 5.06)	51 (1 study)	⊕⊕⊖⊖ **Low**[1]	-
	111 per 1000	**124 per 1000** (28 to 562)				
	Moderate					
	111 per 1000	**124 per 1000** (28 to 562)				
Incidence of herpes labialis during use of the preventative intervention (by clinical evaluation) - experimental ultraviolet light	**Study population**		**RR 0.07** (0.01 to 0.33)	111 (2 studies)	⊕⊖⊖⊖ **Very low**[2]	-
	456 per 1000	**32 per 1000** (5 to 151)				

	Moderate					
	487 per 1000	**34 per 1000** (5 to 161)				
Incidence of herpes labialis during use of the preventative intervention (by culture)	**Study population**		See comment	73 (1 study)	⊕⊖⊖⊖ **Very low**[3]	Risks were calculated from pooled risk differences
	658 per 1000	**26 per 1000** (0 to 191)				
	Moderate					
	658 per 1000	**26 per 1000** (0 to 191)				

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **GRADE:** Grading of Recommendations Assessment, Development and Evaluation; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded two levels due to risk of bias and imprecision: the available evidence is limited to a single study with a high risk of reporting bias.
[2]Downgraded three levels due to imprecision and multiple risk of bias in performance, detection, and reporting. The available evidence is from two trials with a high risk of biases.
[3]Downgraded three levels due to imprecision and multiple risk of bias in performance, detection, and reporting: the available evidence is from a single trial with a high risk of biases.

Summary of findings 14. Interferon compared with placebo for prevention of herpes labialis

Interferon compared with placebo for prevention of herpes labialis

Patient or population: participants with recurrent herpes labialis
Settings: hospitals
Intervention: interferon
Comparison: placebo

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**Number of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				

	Placebo	Interferon				
Incidence of herpes labialis during use of the preventative intervention - presurgical	**Study population**		**RR 1.59** (1.05 to 2.41)	32 (1 study)	⊕⊕⊖⊖ **Low**[1, 2]	-
	571 per 1000	**909 per 1000** (600 to 1000)				
	Moderate					
	571 per 1000	**908 per 1000** (600 to 1000)				
Incidence of herpes labialis during use of the preventative intervention - postsurgical	**Study population**		**RR 0.99** (0.59 to 1.66)	44 (1 study)	⊕⊕⊖⊖ **Low**[1, 2]	-
	571 per 1000	**566 per 1000** (337 to 949)				
	Moderate					
	571 per 1000	**565 per 1000** (337 to 948)				
Incidence of herpes labialis during use of the preventative intervention - pre- and postsurgical	**Study population**		**RR 0.57** (0.34 to 0.95)	37 (1 study)	⊕⊕⊖⊖ **Low**[1, 2]	-
	833 per 1000	**475 per 1000** (283 to 792)				
	Moderate					
	833 per 1000	**475 per 1000** (283 to 791)				
Adverse effects during use of the preventative intervention (fever) - presurgical	**Study population**		**RR 2.45** (1.26 to 4.78)	32 (1 study)	⊕⊕⊕⊖ **Moderate**[2]	-
	333 per 1000	**817 per 1000** (420 to 1000)				
	Moderate					
	333 per 1000	**816 per 1000** (420 to 1000)				
Adverse effects during use of the preventative inter-	**Study population**		**RR 1.96** (1 to 3.84)	44 (1 study)	⊕⊕⊕⊖ **Moderate**[2]	-

vention (fever) - postsurgical	**333 per 1000**	**653 per 1000** (333 to 1000)				
	Moderate					
	333 per 1000	**653 per 1000** (333 to 1000)				
Adverse effects during use of the preventative intervention (fever) - pre- and postsurgical	**Study population**		**RR 11.76** (0.71 to 195.11)	38 (1 study)	⊕⊕⊕⊖ **Moderate**[2]	-
	0 per 1000	**0 per 1000** (0 to 0)				
	Moderate					
	0 per 1000	**0 per 1000** (0 to 0)				

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **GRADE:** Grading of Recommendations Assessment, Development and Evaluation; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level due to inconsistency: the effects of presurgical, postsurgical, and continuous pre- and postsurgical administration of interferon were inconsistent.
[2]Downgraded one level due to imprecision: the available evidence is from a single trial.

Summary of findings 15. Gamma globulin compared with histamine (control) for prevention of herpes labialis

Gamma globulin compared with histamine (control) for prevention of herpes labialis

Patient or population: participants with recurrent herpes labialis
Settings: single centre
Intervention: gamma globulin
Comparison: histamine (control)

Outcomes	Illustrative comparative risks* (95% CI)	Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments

	Assumed risk	Corresponding risk				
	Histamine (control)	Gamma globulin				
Duration of attack of recurrent herpes labialis during use of the preventative intervention	-	The mean duration of attack of recurrent herpes labialis during use of the preventative intervention in the intervention groups was **0.7 higher** (0.55 lower to 1.95 higher)	-	72 (1 study)	⊕⊕⊖⊖ **Low**[1]	-
Severity of attack of recurrent herpes labialis during use of the preventative intervention (less severe recurrences than usual)	**Study population**		**RR 0.97** (0.74 to 1.28)	73 (1 study)	⊕⊕⊖⊖ **Low**[1]	-
	750 per 1000	**728 per 1000** (555 to 960)				
	Moderate					
	750 per 1000	**728 per 1000** (555 to 960)				

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **GRADE:** Grading of Recommendations Assessment, Development and Evaluation; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded two levels due to risk of bias and imprecision: the available evidence is from a single trial with a high risk of reporting bias.

Summary of findings 16. Thymopentin compared with placebo for prevention of herpes labialis

Thymopentin compared with placebo for prevention of herpes labialis
Patient or population: participants with recurrent herpes labialis **Settings:** medical centres **Intervention:** thymopentin **Comparison:** placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Thymopentin				
Incidence of herpes labialis during use of the preventative intervention	0.9 (range 0.1 to 2.0)	Median 0.2 (range 0.0 to 2.7)	-	36 (1 study)	⊕⊕⊕⊖ **Moderate**[1]	P = 0.0027 using the Mann-Whitney test by the trialists
Adverse effects during use of the preventative intervention	**111 per 1000**	**222 per 1000** (47 to 1000)	**RR 2** (0.42 to 9.58)	36 (1 study)	⊕⊕⊕⊖ **Moderate**[1]	-

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **GRADE:** Grading of Recommendations Assessment, Development and Evaluation; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level due to imprecision: the available evidence is from a single trial.

Summary of findings 17. HSV vaccination compared with placebo for prevention of herpes labialis

HSV vaccination compared with placebo for prevention of herpes labialis

Patient or population: participants with recurrent herpes labialis
Settings: university hospitals
Intervention: HSV vaccination
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	HSV vaccination				
Incidence of herpes labialis during use of	1.3 recurrences in a 4-month period	1.6 recurrences in a 4-month period	P = 0.10 calculated by the trialists	64 (1 study)	⊕⊕⊕⊖ **Moderate**[1]	-

the preventative intervention						
Adverse effects during use of the preventative intervention	13 adverse events per 100 injections	22 adverse events per 100 injections	**RR 0.33** (0.01 to 7.45)	64 (1 study)	⊕⊕⊕⊖ **Moderate**[1]	Several adverse events might have occurred in the same participant; no statistical tests were conducted by the trialists

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **GRADE:** Grading of Recommendations Assessment, Development and Evaluation; **HSV:** herpes simplex virus; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level due to imprecision: the available evidence is from a single trial.

Summary of findings 18. Yellow fever vaccination compared with placebo for prevention of herpes labialis

Yellow fever vaccination compared with placebo for prevention of herpes labialis

Patient or population: participants with recurrent herpes labialis
Settings: hospital
Intervention: yellow fever vaccination
Comparison: placebo

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**Number of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Placebo	**Yellow fever vaccination**				
Incidence of herpes labialis during use of the preventative intervention	See comment	See comment	-	1 (1 study)	⊕⊕⊕⊖ **Moderate**[1]	-
Adverse effects during use of the preventative intervention	**83 per 1000**	**28 per 1000** (1 to 621)	**RR 0.33** (0.01 to 7.45)	24 (1 study)	⊕⊕⊕⊖ **Moderate**[1]	-

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **GRADE:** Grading of Recommendations Assessment, Development and Evaluation; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level due to imprecision: the available evidence is from a single trial.

Summary of findings 19. Laser compared with no interventions for prevention of herpes labialis

Laser compared with no interventions for prevention of herpes labialis

Patient or population: participants with recurrent herpes labialis
Settings: university hospitals
Intervention: laser
Comparison: no interventions

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No interventions	Laser				
Incidence of herpes labialis during use of the preventative intervention	0.116 recurrences per month	0.076 recurrences per month	Not estimable	71 (1 study)	⊕⊖⊖⊖ **Very low**[1]	P = 0.076, calculated using the Mann-Whitney U test by the trialists
Adverse effects during use of the preventative intervention	0	0	Not estimable	119 (2 studies)	⊕⊕⊖⊖ **Low**[2]	No adverse events were observed in either group

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **GRADE:** Grading of Recommendations Assessment, Development and Evaluation; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded three levels due to imprecision: the evidence is from a single trial with a high risk of performance and detection biases.
[2]Downgraded two levels due to risk of bias and imprecision: the evidence is from two trials with a high risk of biases.

Summary of findings 20. Hypnotherapy compared with control for prevention of herpes labialis

Hypnotherapy compared with control for prevention of herpes labialis

Patient or population: participants with recurrent herpes labialis
Settings: psychological institute
Intervention: hypnotherapy
Comparison: control

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Hypnotherapy				
Incidence of herpes labialis during use of the preventative intervention (change in frequency of recurrence)	-	The mean incidence of herpes labialis during use of the preventative intervention (change in frequency of recurrence) in the intervention groups was **6.5 lower** (8.76 to 4.24 lower)	-	21 (1 study)	⊕⊖⊖⊖ **Very low**[1]	-
Severity of attack of recurrent herpes labialis during use of the preventative intervention (change in intensity)	-	The mean severity of attack of recurrent herpes labialis during use of the preventative intervention (change in intensity) in the intervention groups was **9.7 lower** (12.46 to 6.94 lower)	-	21 (1 study)	⊕⊖⊖⊖ **Very low**[1]	-
Change in severity (pain) of herpes labialis	-	The mean change in severity (pain) of herpes labialis in the intervention groups was **2.2 lower** (3.14 to 1.26 lower)	-	21 (1 study)	⊕⊖⊖⊖ **Very low**[1]	-
Change in severity (impairment of appearance) of herpes labialis	-	The mean change in severity (impairment of appearance) of herpes labialis in the intervention groups was **1.6 lower** (2.5 to 0.7 lower)	-	21 (1 study)	⊕⊖⊖⊖ **Very low**[1]	-

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **GRADE:** Grading of Recommendations Assessment, Development and Evaluation.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded three levels due to imprecision (the evidence is from a single trial) with a high risk of performance and detection biases.

BACKGROUND

Description of the condition

A virus that resides in the skin of the lips causes herpes simplex labialis (HSL) (Higgins 1993). Its manifestation on the skin is also known as a 'cold sore' or 'fever blister'. The initial infection with the virus, which is called herpes simplex virus (HSV), is by direct contact between the mucous membranes or abraded skin of the lips or mouth and the saliva or other secretions of a person with active primary or recurrent infection (Higgins 1993). Primary infection with HSV typically occurs in early childhood, often with no symptoms, but primary HSV infection may also present as herpetic gingivostomatitis, which is characterised by oral and perioral vesicles (tiny blisters) and ulcers (Higgins 1993). It has been reported that when clinical disease is not present, the virus spreads through respiratory droplets or through interaction with the mucocutaneous releases of an asymptomatic person shedding the virus (Fatahzadeh 2007). Following the primary infection, the virus resides in the sensory ganglia (nerve endings) in a latent form (Higgins 1993). After reactivation, HSV migrates from these sensory ganglia to the outer layer of the skin of the lips or mouth to cause recurrent HSL (Fatahzadeh 2007). Herpes simplex virus type 1 (HSV-1) causes recurrent HSL. Although herpes simplex virus type 2 (HSV-2) may occasionally cause primary oral infection, it rarely causes recurrent HSL (Fatahzadeh 2007).

Herpes simplex labialis affects the lips, with the outer third of the lower lip being most frequently affected (Marques 2003). In up to 60% of affected people, HSL is preceded by warning signs, which are known as 'prodromal symptoms'; these are feelings of pain, burning, itching, or tingling at the site of subsequent vesicle development. Headache may also occur in the prodromal stage (Joseph 1985). Within 24 hours of the prodrome, multiple grouped vesicles appear and then weep until they finally form crusts (Fatahzadeh 2007). Such crusts can often bleed quite easily, forming unsightly blackish crusts due to dried blood, which can bleed again when the skin is stretched, e.g., when smiling (Fatahzadeh 2007). These usually heal without scarring within 5 to 15 days (Marques 2003). Herpes simplex labialis may cause pain, discomfort, inconvenience, and some amount of psychological and social distress as a result of cosmetic disfigurement (Fatahzadeh 2007).

Herpes simplex labialis occurs worldwide and is a very common disease (Higgins 1993). The lifetime prevalence of recurrent herpes labialis is 20% to 52.5% (Celik 2013; Higgins 1993). It has been estimated that there are 98 million cases of HSL each year in the US alone (Higgins 1993). Most people with recurrent HSL have fewer than 2 episodes per year, but 5% to 10% of affected people have a minimum of 6 recurrences per annum (Celik 2013; Rooney 1993). Recurrences of HSL seem to be precipitated by a number of factors, including ultraviolet light (UVL); illness; stress; premenstrual tension; severe drug eruptions; and surgical procedures, such as dental surgery, neural surgery, and dermabrasion (a cosmetic procedure used to smooth scars) (Celik 2013; Higgins 1993; Shiohara 2013). People with atopic dermatitis who carry filaggrin mutations are prone to recurrent HSL, which may be attributed to their deficient antiviral immune response (Leung 2014; Rystedt 1986).

Description of the intervention

To date, there has been no proven way of eradicating HSV from the body completely. A number of interventions have been proposed for the prevention of recurrent HSL, including oral antivirals, topical antivirals, and sunscreens (Worrall 2009).

Antiviral agents, including aciclovir, famciclovir, penciclovir, and valaciclovir, inhibit DNA polymerase and viral replications. Before converting to the active antiviral triphosphate form, these drugs need to be phosphorylated by enzymes, such as viral thymidine kinase (TK) or host cellular kinases. Compared with aciclovir, famciclovir and valaciclovir have greater bioavailability and need less frequent dosing. Foscarnet inhibits viral DNA polymerase independent of phosphorylation and is thus used in aciclovir-resistant HSV infections (Fatahzadeh 2007).

The active ingredients of sunscreens are generally classified into inorganic and organic UVL filters. Inorganic filters, such as titanium oxide, reflect or scatter UVL, while organic filters absorb UVL and convert the energy into heat. The most frequently-used efficacy index of sunscreen in preventing sunburns is the sun protection factor (SPF), which is measured after application of 2 mg/cm^2 of product (Kullavanijaya 2005).

How the intervention might work

Long-term prophylactic administration of oral antivirals (e.g., aciclovir, famciclovir, and valaciclovir) is expected to prevent reactivation of HSV (Worrall 2009). However, continuous daily intake of antivirals is not only costly but also requires the person to adhere to such a programme consistently (Fatahzadeh 2007). Therefore, it is important to design an optimal regimen, balancing known effectiveness of any preventative intervention with the inconvenience and possible side-effects of continuous medication.

When topical aciclovir cream is used as a treatment for HSL, the frequency of application is five times daily (four hours apart except for sleep) (GSK 2008). However, the efficacy and frequency of application when used as a preventative intervention is unclear.

Based on the fact that ultraviolet light induces the recurrence of HSL (Higgins 1993), sunscreens, theoretically, can prevent recurrence of HSL. However, commercially available sunscreens vary greatly in their active ingredients and the effectiveness of their photoprotection. The effectiveness of photoprotection also depends on the appropriate application of sunscreens; frequency of re-application after sweating or water sports (Kullavanijaya 2005); and in the case of lips, eating or drinking (Rooney 1991). In actual use, most people apply less than the amounts used in testing SPF, which compromises the efficacy of the sunscreen (Kullavanijaya 2005). Photoprotective lipscreens often contain less UVL-absorbing ingredients than skin sunscreens (Wahie 2007).

Why it is important to do this review

There has been a Cochrane review on the effects of systemic aciclovir for primary herpetic gingivostomatitis (Nasser 2008) and another on the interventions for the prevention and treatment of HSV in people being treated for cancer (Glenny 2009). However, a systematic review on interventions for preventing HSL in those who are immunocompetent is lacking. We aimed to conduct such a review in order to find out the best evidence on the effects of those

interventions currently available for the prevention of recurrent HSL.

The plans for this review were published as a protocol 'Interventions for prevention of herpes simplex labialis (cold sores on the lips)' (Chi 2012).

OBJECTIVES

To assess the effects of interventions for the prevention of HSL in people of all ages.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) of systemic, topical, and physical interventions for the prevention of herpes simplex labialis (HSL).

Types of participants

Anyone who was immunocompetent and had been initially diagnosed with recurrent HSL by a healthcare professional or trained researcher.

Types of interventions

Any systemic, topical, or physical intervention used for the prevention of HSL. The interventions could be either a single intervention or a combination of interventions. When there were different lengths of use of the intervention, we regarded those of ≤ 1 month as short-term use and those of > 1 month as long-term use. The controls might be a placebo, no intervention, or another active intervention.

Types of outcome measures

Primary outcomes

1. Incidence of HSL during use of the preventative intervention. We accepted both researcher-diagnosed and participant-reported recurrences.
2. Adverse effects during use of the preventative intervention.

Secondary outcomes

1. Duration of attack of recurrent HSL during use of the preventative intervention.
2. Severity (lesion area, stage, pain) of attack of recurrent HSL during use of the preventative intervention.
3. Viral load in saliva.
4. Rate of adherence to the regimen of the preventative intervention.
5. Incidence of HSL after use of the preventative intervention. We accepted both researcher-diagnosed and participant-reported recurrences.
6. Duration of attack of recurrent HSL after use of the preventative intervention.
7. Severity (lesion area, stage, pain) of attack of recurrent HSL after use of the preventative intervention.

Search methods for identification of studies

We aimed to identify all relevant RCTs regardless of language or publication status (published, unpublished, in press, or in progress).

Electronic searches

We searched the following databases up to 19 May 2015:

- the Cochrane Skin Group Specialised Register using the search strategy in Appendix 1;
- the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (Issue 4, 2015) using the strategy in Appendix 2;
- MEDLINE via Ovid (from 1946) using the strategy in Appendix 3;
- EMBASE via Ovid (from 1974) using the strategy in Appendix 4; and
- LILACS (Latin American and Caribbean Health Science Information database, from 1982) using the strategy in Appendix 5.

We searched the Cochrane Oral Health Group Specialised Register using the search strategy in Appendix 1 up to 19 May 2015.

On 22 May 2015, we searched the China National Knowledge Infrastructure (CKNI) database (from 1994) using the strategy in Appendix 6 and Airiti Library (publications and theses from Taiwan, from 1991) using the strategy in Appendix 7.

Trials registers

We searched the following trials databases on 25 May 2015 using the strategy in Appendix 8.

- The US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov).
- The Australian New Zealand Clinical Trials Registry (www.anzctr.org.au).
- The World Health Organization International Clinical Trials Registry platform (www.who.int/trialsearch).
- The EU Clinical Trials Register (www.clinicaltrialsregister.eu).

We searched the metaRegister of Controlled Trials (www.controlled-trials.com) on 13 June 2014, but this was closed and under review when we updated our search on 25 May 2015.

Searching other resources

Reference lists

We scanned the bibliographies of the included studies and published reviews for further references to relevant trials.

Unpublished literature

We tried to identify further unpublished trials through correspondence with the original researchers of the included studies.

Adverse effects

We did not run separate searches for adverse effects of the target interventions. However, we did extract relevant data from the included trials that we identified.

Data collection and analysis

Some parts of this section uses text that was originally published in another Cochrane review (Chi 2011). We included 'Summary of findings' tables where we used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the quality of the evidence for the primary outcomes for the treatment comparisons.

Selection of studies

Two authors (CC and SW) independently checked titles and abstracts identified from the searches. The authors were not blinded to the names of the original researchers, journals, or institutions. If it was clear from the abstract that the study did not refer to a RCT on interventions for prevention of HSL, we excluded it. The same two authors independently assessed the full text version of each remaining study to determine whether it met the predefined selection criteria. We resolved any disagreement by discussion with referral to a third author (FW), if necessary. We listed the studies that we could only exclude after reading the full text and reasons for exclusion in the 'Characteristics of excluded studies' tables.

Data extraction and management

Two authors (CC and SW) independently extracted the data using a specialised data extraction form. We resolved discrepancies by discussion with a third author (FW). One author (CC) entered the data into Review Manager (RevMan) (Review Manager 2014).

Assessment of risk of bias in included studies

We evaluated the following components since there is some evidence that these are associated with biased estimates of intervention effect (Higgins 2011):

1. random sequence generation - adequacy of the method of random sequence generation to produce comparable groups in every aspect except for the intervention;
2. allocation concealment - adequacy of the method used to conceal the allocation sequence to prevent anyone foreseeing the allocation sequence in advance of, or during, enrolment;
3. blinding of participants and personnel - adequacy of blinding study participants and researchers from knowledge of the allocated interventions;
4. blinding of outcome assessment - adequacy of blinding outcome assessors from knowledge of the allocated interventions;
5. incomplete outcome data - the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis, whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomised participants), reasons for attrition/exclusions where reported, and any re-inclusions in our analyses;
6. selective reporting - whether all prespecified outcomes were reported when the trial protocol was available; and
7. other sources of bias - any other important concerns about bias.

Measures of treatment effect

For dichotomous outcomes, we expressed the results as risk ratios (RR) with 95% confidence intervals (CI) and where appropriate as number needed to treat to benefit (NNTB) with 95% CI and the baseline risk to which it applies. For continuous outcomes, we expressed the results as difference in means (MD) with 95% CI or where different outcome scales were pooled as standardised mean differences (SMD) with 95% CI. For time-to-event outcomes, we expressed the results as hazard ratios (HRs). If Kaplan-Meier curves were presented, we would have extracted the data from the graphs and calculated HRs according to the methods given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). However, time-to-event outcomes were treated as continuous data in a few included trials. We therefore could only present the original data reported.

With regard to our primary outcome 'Adverse effects during use of the preventative intervention', we measured this by assessing the proportion of participants who experienced adverse events.

With regard to our secondary outcome 'Rate of adherence to the regimen of the preventative intervention', we measured this by assessing either the proportion of participants who adhered to the interventions or the mean proportion of interventions participants received.

Unit of analysis issues

All randomised participants in the control and intervention groups were the unit of analysis. We did not pool the following types of studies with studies of other designs.

Cluster-randomised trials

For cluster-randomised trials, we would have used appropriate techniques described in section 16.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Cross-over trials

For cross-over trials, we used appropriate techniques described in section 16.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Studies with multiple treatment groups

Where there were multiple intervention groups within a trial, we made pair-wise comparisons of an intervention versus no intervention, placebo, or another active intervention.

Dealing with missing data

We contacted the original researchers of studies less than 15 years old for missing data (Table 1). When the missing data were not available, we initially assumed those data were missing at random. If the missing data were caused by participants' dropout, we conducted intention-to-treat analyses. For dichotomous outcomes, we would have regarded participants with missing outcome data as treatment failures and included them in the analyses. For continuous outcomes, we would have carried forward the last recorded value for participants with missing outcome data. Where high levels of missing data were seen within the analyses, we would have conducted sensitivity analyses to assess the robustness of the results from the approach described above by comparing the results with those that exclude the missing data from the analyses. However, we failed to conduct the planned analyses because of lacking adequate data, for example, the respective number of randomised participants and those who were lost to follow up in each group.

Assessment of heterogeneity

We assessed clinical heterogeneity inherent in the study design, interventions, participants, and outcome measures to determine whether a meta-analysis was appropriate. The anticipated clinical heterogeneity included various lengths and regimens of the same intervention, presence of atopic dermatitis, and induction by UVL. We also determined the I^2 statistic to assess the statistical heterogeneity. When there was clinical heterogeneity or the I^2 statistic was greater than 80%, we did not perform a meta-analysis.

Assessment of reporting biases

We would have tested publication bias for primary outcomes by using a funnel plot when at least 10 trials on an intervention were available. However, the limited number of trials for each intervention meant it was impossible to do this test.

Data synthesis

For trials on a particular intervention, we conducted a meta-analysis using a random-effects model (DerSimonian and Laird model) to calculate a weighted intervention effect across trials when the I^2 statistic was 80% or less with reasonable clinical homogeneity. We decided clinical homogeneity based on similar participants and intervention regimens. Where it was inappropriate or impossible to perform a meta-analysis, we summarised the data narratively for each trial.

Subgroup analysis and investigation of heterogeneity

We discussed similarities and differences of included RCTs in terms of the study design, interventions, participants, and outcome measures. We would have conducted subgroup analyses of the following if adequate data were available:

- participants with atopic dermatitis: we found no data relevant to atopic dermatitis and thus did not conduct a subgroup analysis; and
- participants with UVL-induced HSL: for sunscreen where relevant data were available, we conducted a subgroup analysis on HSL induced by natural and experimental UVL separately.

Sensitivity analysis

We would have performed a sensitivity analysis to examine the intervention effects after excluding those studies with lower methodological quality if appropriate. However, we did not do so because of a very limited number of trials for the same intervention.

Other

We involved a consumer coauthor (FD) throughout the review process to help improve the relevance and readability of the final review.

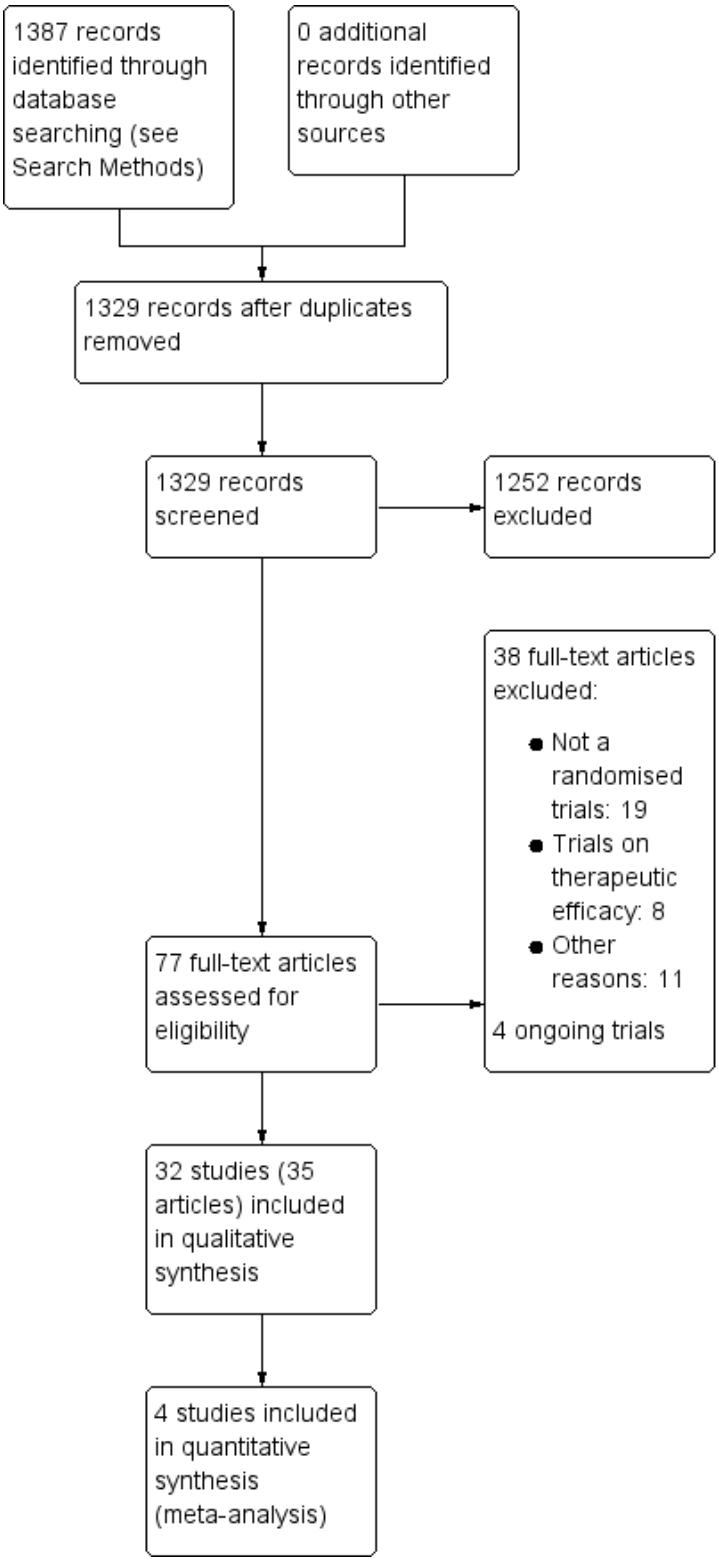
RESULTS

Description of studies

Results of the search

As shown in Figure 1, our search identified 1387 citations. After removing duplicates, we assessed 1329 citations. We excluded 1252 citations because the title, abstract, or both did not meet our inclusion criteria. We sought the full texts of the remaining 77 citations. We excluded 38 citations, mostly because these were either non-randomised studies or randomised controlled trials (RCTs) on interventions for treatments of herpes simplex labialis (HSL). Of the remaining 39 citations, we transferred 4 studies to the section 'Ongoing studies' as they were not yet completed. We included the remaining 35 citations, reporting 32 relevant trials, in this review. One included citation reported four trials, of which three met our inclusion criteria (Spruance 1991a; Spruance 1991b; Spruance 1991c). Five included trials, Miller 2004; Pazin 1979; Pedersen 2001; Russell 1978; Schindl 1999, had two citations.

Figure 1. Study flow diagram.



Included studies

This review included 32 trials, with a total of 2640 participants, covering 19 treatments. We describe the details of the included studies in the 'Characteristics of included studies' tables.

Design

All of the 32 included studies were RCTs, with 5 being cross-over RCTs (Gibson 1986; Gilbert 2007; Rooney 1991; Rooney 1993; Thein 1984).

Sample sizes

The number of participants in the included studies ranged from 19 to 310. Seven of the included trials had a small sample size of less than 30 participants (Duteil 1998; Gibson 1986; Møller 1997; Pfitzer 2005; Rooney 1993; Thein 1984).

Setting

The setting was multicentre in 13 trials (Altmeyer 1991; Bernstein 1994; Bernstein 1997; Bolla 1985; Busch 2009; Gibson 1986; Mills 1987; Raborn 1997; Raborn 1998; Rooney 1991; Spruance 1988; Spruance 1991c; Spruance 1999) and single-centre in 19 trials (Baker 2003; de Carvalho 2010; Duteil 1998; Gilbert 2007; Ho 1984; Miller 2004; Møller 1997; Pazin 1979; Pedersen 2001; Pfitzer 2005; Redman 1986; Rooney 1993; Russell 1978; Schädelin 1988; Schindl 1999; Senti 2013; Spruance 1991a; Spruance 1991b; Thein 1984). All of the included trials were conducted either in Europe or North America.

Participants

All of the included trials included adults aged 18 years or older, with 2 trials extending to persons aged 16 years or older, Bolla 1985; Gibson 1986, and 1 trial extending to persons aged at least 12 years (Miller 2004). Two trials, Russell 1978; Thein 1984, did not state the age limit of inclusion criteria but included participants aged seven and eight years, respectively.

Interventions

The included trials assessed the effects of 19 interventions for preventing HSL, including 6 oral treatments (aciclovir (Raborn 1998; Rooney 1993; Schädelin 1988; Spruance 1988; Spruance 1991a; Spruance 1991b), valaciclovir (Baker 2003; Gilbert 2007; Miller 2004), famciclovir (Spruance 1999), levamisole (Russell 1978), lysine (Thein 1984), and LongoVital® (a vitamin and herbs supplement) (Pedersen 2001)), 5 topical treatments (aciclovir cream (Gibson 1986; Raborn 1997; Spruance 1991c), aciclovir plus 348U87 cream (Bernstein 1994), topical foscarnet 3% (Bernstein 1997), 1,5-pentanediol (a low-toxicity molecule with an antiviral activity) gel (Busch 2009), 2-hydroxypropyl-β-cyclo dextrin gel (Senti 2013)), sunscreens (Duteil 1998; Mills 1987; Rooney 1991), 3 immunomodulating treatments given by injection (interferon (Ho 1984; Pazin 1979), intradermal gamma globulin (Redman 1986), and thymopentin (Bolla 1985)), 2 vaccines (herpes simplex virus (HSV) type I subunit vaccine (Altmeyer 1991) and yellow fever vaccination (Møller 1997)), low-intensity lasers (de Carvalho 2010; Schindl 1999), and hypnotherapy (Pfitzer 2005).

Outcomes

Of the 32 included trials, all reported either the incidence or frequency of HSL during use of the preventative intervention, and 17 trials (53%) reported adverse events. There were 12 and 20 trials reporting the duration and severity of recurrent HSL, respectively. Only one trial, Miller 2004, measured the shedding of HSV in the saliva, and only two trials, Rooney 1993; Spruance 1999, assessed participants' adherence to study medications.

Funding source

Of the included 32 trials, industry supported 18, and non-profit organisations (such as government or academic institutions) supported 4; the other 10 trials did not report the funding source.

Excluded studies

We excluded 38 citations after examining the full text. We list the reasons for exclusion in the 'Characteristics of excluded studies' tables.

Ongoing Studies

We identified 4 ongoing trials that were on a sheabutter extract (BSP110), botulinum toxin A injection, an experimental drug (BTL-TML-HSV), and squaric acid dibutylester, respectively (ISRCTN03397663; NCT01225341; NCT01902303; NCT01971385). We contacted the four trialists, but none of them replied. We present the details of these trials in the 'Characteristics of ongoing studies' tables.

Risk of bias in included studies

We summarise our judgements about each 'Risk of bias' item presented as percentages across all of the included trials in Figure 2, and we summarise our judgements about each 'Risk of bias' item for each included trial in Figure 3. We present further details in the 'Risk of bias' tables in the 'Characteristics of included studies' section. The risk of bias of the included trials varied from low to high.

Figure 2. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies.

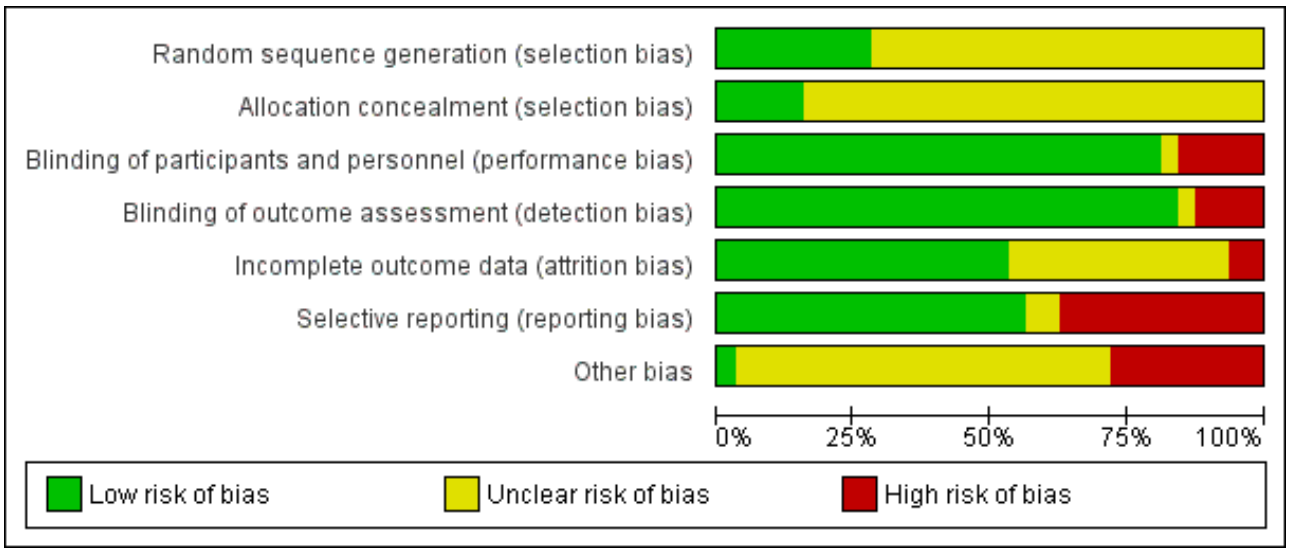


Figure 3. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study.

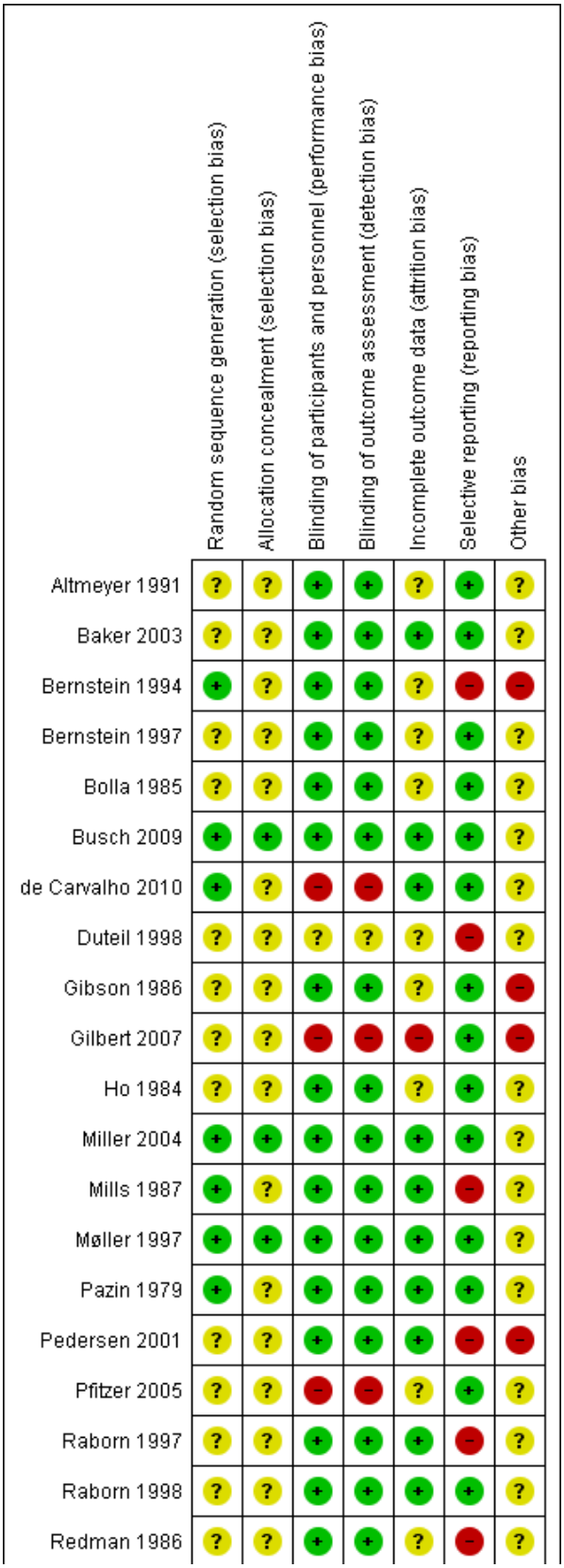
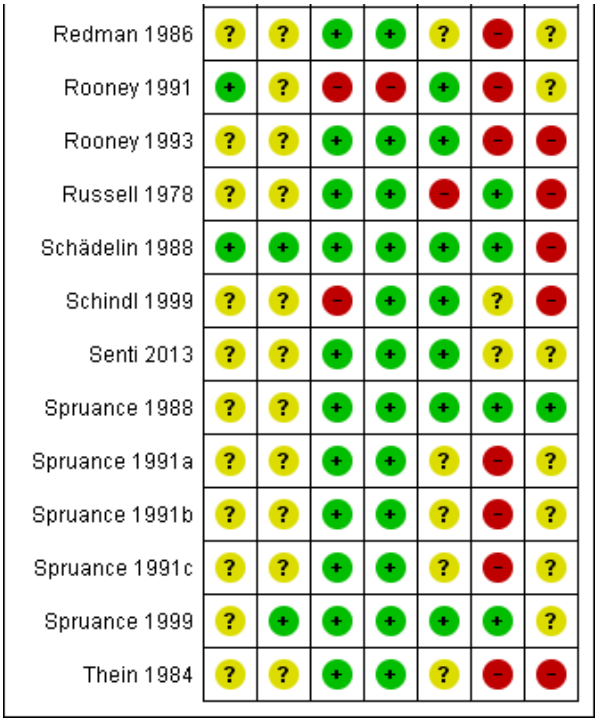


Figure 3. (Continued)



Allocation

Nine trials used an adequate method of generation of the randomisation sequence (Bernstein 1994; Busch 2009; de Carvalho 2010; Miller 2004; Mills 1987; Møller 1997; Pazin 1979; Rooney 1991; Schädelin 1988), but all the other 23 trials did not describe the process of randomisation.

Allocation could not be foreseen in 5 trials (Busch 2009; Miller 2004; Møller 1997; Schädelin 1988; Spruance 1999), while it was unclear if allocation was concealed in the other 27 trials.

Blinding

Twenty-six trials blinded both the investigators and participants (Altmeyer 1991; Baker 2003; Bernstein 1994; Bernstein 1997; Bolla 1985; Busch 2009; Gibson 1986; Ho 1984; Miller 2004; Mills 1987; Møller 1997; Pazin 1979; Pedersen 2001; Raborn 1997; Raborn 1998; Redman 1986; Rooney 1993; Russell 1978; Schädelin 1988; Senti 2013; Spruance 1988; Spruance 1991a; Spruance 1991b; Spruance 1991c; Spruance 1999; Thein 1984), while 5 trials did not blind them (de Carvalho 2010; Gilbert 2007; Pfitzer 2005; Rooney 1991; Schindl 1999). The de Carvalho 2010 trial compared laser treatments with no interventions. The Schindl 1999 trial performed the placebo irradiation in the same manner as in the laser group except that the laser was not turned on. However, laser irradiation might produce the sensation of sound and heat that could have been sensed by the participants. The Gilbert 2007 trial compared episodic and suppressive valaciclovir regimens. The Pfitzer 2005 trial compared hypnotherapy with no hypnotherapy. The Rooney 1991 trial compared a sunscreen with placebo solution, but the placebo recipients had sunburn while none of the sunscreen recipients had sunburn. Thus, the participants and researchers might have known the assigned treatments. It was unclear if the investigators and participants were blinded in the Duteil 1998 trial.

Outcome assessment was blinded in 27 trials (Altmeyer 1991; Baker 2003; Bernstein 1994; Bernstein 1997; Bolla 1985; Busch 2009; Gibson 1986; Ho 1984; Miller 2004; Mills 1987; Møller 1997; Pazin 1979; Pedersen 2001; Raborn 1997; Raborn 1998; Redman 1986; Rooney 1993; Russell 1978; Schädelin 1988; Schindl 1999; Senti 2013; Spruance 1988; Spruance 1991a; Spruance 1991b; Spruance 1991c; Spruance 1999; Thein 1984) and unblinded in 4 trials (de Carvalho 2010; Gilbert 2007; Pfitzer 2005; Rooney 1991). It was unclear if the outcome assessors were blinded in the other trial (Duteil 1998).

Incomplete outcome data

The risk of attrition bias was low in 17 trials because of a low or null dropout rate (Baker 2003; Busch 2009; de Carvalho 2010; Miller 2004; Mills 1987; Møller 1997; Pazin 1979; Pedersen 2001; Raborn 1997; Raborn 1998; Rooney 1991; Rooney 1993; Schindl 1999; Schädelin 1988; Senti 2013; Spruance 1988; Spruance 1999). On the other hand, the risk of attrition bias was high in two trials because of a high dropout rate (Gilbert 2007; Russell 1978). No dropouts or withdrawals were mentioned in the other 13 trials.

Selective reporting

A total of 18 trials reported both the prespecified primary efficacy and adverse outcomes (Altmeyer 1991; Baker 2003; Bernstein 1997; Bolla 1985; Busch 2009; de Carvalho 2010; Gibson 1986; Gilbert 2007; Ho 1984; Miller 2004; Møller 1997; Pazin 1979; Pfitzer 2005; Raborn 1998; Russell 1978; Schädelin 1988; Spruance 1988; Spruance 1999). We judged these 18 trials to be at a low risk of reporting bias.

The Schindl 1999 trial reported the median recurrence-free interval, which was not a prespecified outcome in our review protocol. The study protocol of the Senti 2013 trial is available on the US National Institutes of Health ongoing trials register (identifier: NCT00914745). The prespecified primary outcome (the number of herpes labialis relapse) has been reported. However, the exact numerical data were not provided; the authors only provided the data in plots. We therefore judged the two trials to be at an unclear risk of bias.

A total of 10 trials did not report adverse events (Bernstein 1994; Duteil 1998; Mills 1987; Redman 1986; Rooney 1991; Rooney 1993; Spruance 1991a; Spruance 1991b; Spruance 1991c; Thein 1984). The Pedersen 2001 and Raborn 1997 trials did not fully report the details of outcome data. All of these 12 trials were marked as high risk of bias for this domain.

Other potential sources of bias

A total of nine trials had a high risk of other potential bias for various reasons including early termination (Bernstein 1994), no washout period (Gibson 1986; Gilbert 2007; Rooney 1993; Thein 1984), different baseline frequency of recurrence of HSL (Pedersen 2001; Russell 1978), lack of standardised follow-up plan (Schindl 1999), and a low percentage of participants having a history of HSL (Schädelin 1988). We judged Spruance 1988 at a low risk of other potential bias because of the trialists' advice to participants on frequent use of a standard sunscreen and no relation between the occurrence of herpes labialis and the potential confounding factors.

Effects of interventions

See: **Summary of findings for the main comparison** Oral aciclovir (short-term) compared with placebo for prevention of herpes simplex labialis; **Summary of findings 2** Oral aciclovir (long-term) compared with placebo for prevention of herpes simplex labialis; **Summary of findings 3** Valaciclovir (short-term) compared with placebo for prevention of herpes simplex labialis; **Summary of findings 4** Valaciclovir (long-term) compared with placebo for prevention of herpes labialis; **Summary of findings 5** Valaciclovir (suppressive regimen compared with episodic regimen) for prevention of herpes labialis; **Summary of findings 6** Famciclovir compared with placebo for prevention of herpes labialis; **Summary of findings 7** Levamisole compared with placebo for prevention of herpes labialis; **Summary of findings 8** Lysine compared with placebo for prevention of herpes labialis; **Summary of findings 9** Topical aciclovir (short-term) compared with placebo for prevention of herpes labialis; **Summary of findings 10** Topical aciclovir and 348U87 cream (short-term) compared with placebo for prevention of herpes labialis; **Summary of findings 11** Topical foscarnet compared with placebo for prevention of herpes labialis; **Summary of findings 12** Topical 1,5-pentanediol compared with placebo for prevention of herpes labialis; **Summary of findings 13** Sunscreen compared with placebo for prevention of herpes labialis; **Summary of findings 14** Interferon compared with placebo for prevention of herpes labialis; **Summary of findings 15** Gamma globulin compared with histamine (control) for prevention of herpes labialis; **Summary of findings 16** Thymopentin compared with placebo for prevention of herpes labialis; **Summary of findings 17** HSV vaccination compared with placebo for prevention of herpes labialis; **Summary of findings 18** Yellow fever vaccination compared with placebo for prevention of herpes labialis; **Summary of findings 19** Laser compared with no interventions for prevention of herpes labialis; **Summary of findings 20** Hypnotherapy compared with control for prevention of herpes labialis

Our prespecified outcomes were as follows:

- Primary outcomes
  a. Incidence of HSL during use of the preventative intervention. We accepted both researcher-diagnosed and participant-reported recurrences.
  b. Adverse effects during use of the preventative intervention.
- Secondary outcomes
  a. Duration of attack of recurrent HSL during use of the preventative intervention.
  b. Severity (lesion area, stage, pain) of attack of recurrent HSL during use of the preventative intervention.
  c. Viral load in saliva.
  d. Rate of adherence to the regimen of the preventative intervention.
  e. Incidence of HSL after use of the preventative intervention. We accepted both researcher-diagnosed and participant-reported recurrences.
  f. Duration of attack of recurrent HSL after use of the preventative intervention.
  g. Severity (lesion area, stage, pain) of attack of recurrent HSL after use of the preventative intervention.

Not all of the included studies addressed our prespecified outcomes. In which case, we indicated this at the bottom of the section for the specific comparison.

We only provided short-term and long-term subheadings when both short- and long-term data were available. If only one kind of data were available, we described the length of trial in the text.

In general, the quality of the body of evidence is low to moderate, but very low for some outcomes of few interventions. We present the respective judgement of the quality of evidence for each intervention in the 'Summary of findings' tables.

Oral interventions

Oral aciclovir

Short-term (≤ 1 month) use

A total of five trials tested the efficacy of short-term use of oral aciclovir in preventing HSL (Raborn 1998; Schädelin 1988; Spruance 1988; Spruance 1991a; Spruance 1991b). Please see Summary of findings for the main comparison where we judged the quality of the evidence for this comparison as low to moderate for the following outcomes.

Primary outcome 1. Incidence of HSL during use of the preventative intervention

One trial on aciclovir 800 mg twice daily beginning 12 to 24 hours before sun exposure and continuing for the entire sun-exposure period (3 to 7 days), Raborn 1998, found no significant evidence for the prevention of HSL (risk ratio (RR) 1.08, 95% confidence interval (CI) 0.62 to 1.87; n = 237; see Analysis 1.1). Two trials tested the efficacy of 200 mg 5 times daily beginning immediately after, or 7 days before, ultraviolet radiation exposure and continuing for 7 days following the exposure (Spruance 1991a; Spruance 1991b).

The trialists pooled the data from the two trials because of similar results. No significant effects in preventing HSL were found (RR 0.46, 95% CI 0.20 to 1.07; n = 66; see Analysis 1.1). However, aciclovir 400 mg twice daily (starting on the evening prior to surgery or 12 hours prior to the first anticipated sun exposure and continued for 5 to 7 days) significantly reduced the occurrence of HSL either by clinical evaluation (RR 0.26, 95% CI 0.13 to 0.51; n = 177; 2 trials (Schädelin 1988; Spruance 1988); see Analysis 1.1) or culture (RR 0.05, 95% CI 0.00 to 0.70; n = 30; 1 trial (Schädelin 1988); see Analysis 1.2).

Primary outcome 2. Adverse effects during use of the preventative intervention

Three trials, Raborn 1998; Schädelin 1988; Spruance 1988, found no significant differences in adverse events between placebo and aciclovir 800 mg or 400 mg twice daily (aciclovir 800 mg twice daily: RR 0.98, 95% CI 0.70 to 1.38; n = 239; 1 trial; aciclovir 400 mg twice daily: RR 2.30, 95% CI 0.62 to 8.58; n = 183; 2 trials) (see Analysis 1.3).

Secondary outcome 2. Severity (lesion area, stage, pain) of attack of recurrent HSL during use of the preventative intervention

The Raborn 1998 trial found a shorter length and width of the lesion in the placebo group when compared with the aciclovir 800 mg group (see Analysis 1.4), but found no differences in disease stage between the aciclovir 800 mg and placebo groups (see Analysis 1.5). The Spruance 1988 trial found no differences in lesional size and pain between the aciclovir 400 mg and placebo groups (see Analysis 1.4 and Analysis 1.6).

Secondary outcome 5. Incidence of HSL after use of the preventative intervention

The Spruance 1988 trial followed up the participants for 4 weeks after treatment and found no significant difference in the recurrence of HSL after use of the preventative intervention (RR 1.23, 95% CI 0.49 to 3.14; n = 147; see Analysis 1.7).

There were no relevant data for this intervention for our other outcomes.

Long-term (> 1 month) use

Only one cross-over trial assessed the efficacy of 4-month use of oral aciclovir in preventing HSL (Rooney 1993). Please see Summary of findings 2 where we judged the quality of the evidence for this comparison as low for the following outcomes.

Primary outcome 1. Incidence of HSL during use of the preventative intervention

Aciclovir therapy when compared with placebo resulted in a reduced mean of clinically documented recurrences (0.85 versus 1.80 episodes per participant per a 4-month period, P = 0.009) and culture-positive recurrence (0.40 versus 1.40 episodes per participant per a 4-month period, P = 0.003).

When comparing with placebo, Rooney 1993 also found a longer time to first recurrence (which was not a prespecified outcome in this review) during aciclovir treatment (clinically determined recurrence: 46 versus 118 days, P = 0.05; culture-positive recurrence: > 118 versus 46 days, P = 0.002).

Secondary outcome 1. Duration of attack of recurrent HSL during use of the preventative intervention

The Rooney 1993 trial did not prespecify an analysis on the duration of recurrent HSL but did a posthoc comparison and found a marginally shorter duration of recurrent HSL during aciclovir treatment when compared with placebo (difference in means (MD) -3.60, 95% CI -7.20 to 0; n = 40; see Analysis 2.1).

Secondary outcome 4. Rate of adherence to the regimen of the preventative intervention

The rate of adherence to the preventative intervention was very high; the participants took 99% of the prescribed study medication during both aciclovir and placebo treatments.

There were no relevant data for this intervention for our other outcomes.

Valaciclovir

Short-term (≤ 1 month) use

Only one trial, Miller 2004, investigated the effects of a two-day valaciclovir treatment (on the day of dental procedure and the following day) in preventing recurrence of HSL during a one-week observation period. Please see Summary of findings 3 where we judged the quality of the evidence for this comparison as moderate for the following outcomes.

Primary outcome 1. Incidence of HSL during use of the preventative intervention

There was no reduction in the recurrence of HSL either by clinical evaluation (RR 0.55, 95% CI 0.23 to 1.28; n = 125; see Analysis 3.1) or culture confirmation (RR 0.47, 95% CI 0.21 to 1.08; n = 125; see Analysis 3.2).

Primary outcome 2. Adverse effects during use of the preventative intervention

There were no significant differences in adverse events found between the valaciclovir and placebo groups (RR 1.33, 95% CI 0.71 to 2.50; n = 125; see Analysis 3.3).

Secondary outcome 1. Duration of attack of recurrent HSL during use of the preventative intervention

The Miller 2004 trial found that valaciclovir treatment was associated with a significantly shorter time to cessation of pain in comparison with placebo (3.2 versus 6.2 days; P = 0.006; n = 125).

Secondary outcome 2. Severity (lesion area, stage, pain) of attack of recurrent HSL during use of the preventative intervention

There were no significant differences in the clinical severity (1.7 versus 1.9; P = non-significant; n = 125) between the valaciclovir and placebo groups.

Secondary outcome 3. Viral load in saliva

There were no significant differences in the viral load, i.e., HSV-1 shedding in the saliva (RR 0.16, 95% CI 0.02 to 1.26; n = 120; see Analysis 3.4), between the valaciclovir and placebo groups.

There were no relevant data for this intervention for our other outcomes.

Long-term (> 1 month) use

Please see Summary of findings 4 where we judged the quality of the evidence for this comparison as moderate for the following outcomes.

Primary outcome 1. Incidence of HSL during use of the preventative intervention

Only 1 placebo-controlled trial, Baker 2003, assessed the effects of valaciclovir 500 mg once daily for 16 weeks in preventing HSL and found a significantly lower incidence of HSL in the valaciclovir group (0.12 versus 0.21 episodes per participant per month; P = 0.042; n = 95).

Primary outcome 2. Adverse effects during use of the preventative intervention

No differences in adverse events existed between the 2 groups (RR 0.86, 95% CI 0.51 to 1.46; n = 95; see Analysis 4.1).

There were no relevant data for this comparison for our secondary outcomes.

Suppressive regimen versus episodic regimen

A cross-over trial, Gilbert 2007, compared an 'episodic regimen' (two 2 gm doses of valaciclovir separated by 12 hours at the first sign of prodrome) and 'suppressive regimen' (valaciclovir 1 gm once daily) for 6 months, respectively. Please see Summary of findings 5 where we judged the quality of the evidence for this comparison as very low for the following outcomes.

Primary outcome 1. Incidence of HSL during use of the preventative intervention

Compared with the episodic regimen, the suppressive regimen had a significantly lower incidence of HSL (MD -0.10 episodes per participant per month, 95% CI -0.16 to -0.05; n = 120; see Analysis 5.1).

Primary outcome 2. Adverse effects during use of the preventative intervention

There were no significant differences in adverse events between the 2 regimens (RR 1.21, 95% CI 0.78 to 1.87; n = 152; see Analysis 5.2).

Secondary outcome 1. Duration of attack of recurrent HSL during use of the preventative intervention

There were no significant differences in the duration of attack (MD -1.08, 95% CI -2.16 to 0.00; n = 120; see Analysis 5.3) between the 2 regimens.

Secondary outcome 2. Severity (lesion area, stage, pain) of attack of recurrent HSL during use of the preventative intervention

There were no significant differences in the pain (MD -0.09, 95% CI -0.20 to 0.02; n = 120; see Analysis 5.4) and maximal total lesion area (MD -5.38, 95% CI -10.91 to 0.15; n = 120; see Analysis 5.5) between the 2 regimens.

There were no relevant data for this intervention for our other outcomes.

Famciclovir

A placebo-controlled trial, Spruance 1999, assessed the effects of various dosages of famciclovir (125 mg, 250 mg, and 500 mg) 3 times daily for 5 days, beginning 48 hours after ultraviolet radiation exposure in preventing HSL. Please see Summary of findings 6 where we judged the quality of the evidence for this comparison as moderate for the following outcomes.

Primary outcome 1. Incidence of HSL during use of the preventative intervention

The Spruance 1999 trial found no differences in recurrence of HSL between 3 different doses of famciclovir and placebo (n = 243; see Analysis 6.1).

Primary outcome 2. Adverse effects during use of the preventative intervention

No significant differences in adverse events were found between three different doses of famciclovir and placebo. (The trialists did not provide exact numerical data.)

Secondary outcome 1. Duration of attack of recurrent HSL during use of the preventative intervention

The difference in time to healing compared with the placebo group was significantly shorter in the famciclovir 500 mg group (by 2.8 days: hazard ratio (HR) 2.39; 95% CI 1.23 to 4.63; P = 0.010), but not for the other 2 groups (n = 243; see Analysis 6.2).

Secondary outcome 2. Severity (lesion area, stage, pain) of attack of recurrent HSL during use of the preventative intervention

There were no differences in pain between the 3 famciclovir groups and the placebo groups (RR 1.0, 95% CI 0.90 to 1.16; RR 0.92, 95% CI 0.76 to 1.12; and RR 0.90, 95% CI 0.75 to 1.09 for the famciclovir 125 mg, 250 mg, and 500 mg groups, respectively, when compared with the placebo group; n = 102; see Analysis 6.3).

Secondary outcome 4. Rate of adherence to the regimen of the preventative intervention

The rate of adherence was very high: 100% of the participants in all 3 famciclovir groups (n = 183) and 95% of those in the placebo group (n = 60) took all of the prescribed study medication.

There were no relevant data for this intervention for our other outcomes.

Levamisole

Only 1 trial with a high withdrawal rate (27.2%), Russell 1978, evaluated the effects of levamisole in preventing HSL. Please see Summary of findings 7 where we judged the quality of the evidence for this comparison as very low for the following outcomes.

Primary outcome 1. Incidence of HSL during use of the preventative intervention

Among the 72 participants who completed the trial, both the levamisole group and placebo group showed a reduction in the frequency of HSL, but there were no significant differences between the 2 groups (2.1 ± 1.2 versus 2.7 ± 2.3 episodes during a 6-month period). When taking into account the different baseline frequency of HSL (4.8 ± 2.7 and 3.4 ± 1.8 episodes during a 6-month period for the levamisole and placebo group, respectively), levamisole was associated with a greater reduction in the frequency of HSL (MD -2.00, 95% CI -2.24 to -1.76; n = 72; see Analysis 7.1).

Primary outcome 2. Adverse effects during use of the preventative intervention

Of the 99 randomised participants, 27 (27.2%) did not complete the trial because of either adverse events (such as nausea and fever) or lack of efficacy: the trialists' analysis excluded 19 (39.6%) in the levamisole group and 8 (15.7%) in the placebo group. The levamisole group had a significantly higher withdrawal rate than the placebo group (risk difference (RD) 0.24, 95% CI 0.07 to 0.41; n = 99; see Analysis 7.2).

Secondary outcome 1. Duration of attack of recurrent HSL during use of the preventative intervention

Compared with the placebo group, the levamisole group was associated with a lesser reduction in the duration of attack of HSL (MD 0.70, 95% CI 0.22 to 1.18; n = 72; see Analysis 7.3).

There were no relevant data for this intervention for our other outcomes.

Lysine

A placebo-controlled cross-over trial, Thein 1984, investigated the effects of L-lysine monolysine monohydrochloride 1000 mg per day for 6 months in preventing recurrent HSL. Please see Summary of findings 8 where we judged the quality of the evidence for this comparison as very low for the following outcome.

Primary outcomes 1. Incidence of HSL during use of the preventative intervention

Because the Thein 1984 trial lacked a washout period, we used only the data from the first period before cross-over for analysis and found no significant difference in the incidence of recurrent HSL between lysine and placebo treatment (MD -0.04, 95% CI -0.37 to 0.29; n = 26; see Analysis 8.1).

There were no relevant data for this intervention for our other outcomes.

LongoVital®

A placebo-controlled trial, Pedersen 2001, evaluated the effects of daily intake of LongoVital® (a vitamin and herbs supplement) in preventing recurrence of HSL. The treatment period was four months, and the participants were followed up for another four months after stopping the study medications.

Primary outcome 1. Incidence of HSL during use of the preventative intervention

During the treatment period, there were no significant differences in the number of recurrent HSL episodes found between the LongoVital® (LV) and placebo groups (the median being 1.2 and 1.6 during the period 'days 0 to 60' and 0.7 and 1.0 during the period 'days 61 to 120' for the LV and placebo groups, respectively; n = 52).

Secondary outcome 1. Duration of attack of recurrent HSL during use of the preventative intervention

There were no significant differences in the median duration of recurrent HSL episodes between the LongoVital® and placebo groups (the median being 5.0 days and 4.3 days during the period 'days 0 to 60' and 3.0 days and 4.2 days during the period 'days 61 to 120', respectively; n = 52).

Secondary outcome 2. Severity (lesion area, stage, pain) of attack of recurrent HSL during use of the preventative intervention

The maximal size of recurrent HSL lesions did not significantly differ between the LongoVital® and placebo groups (the median being 5.1 mm and 5.0 mm during the period 'days 0 to 60' and 2.5 mm and 5.2 mm during the period 'days 61 to 120', respectively; n = 52).

Secondary outcome 5. Incidence of HSL after use of the preventative intervention

During the post-treatment follow-up period, there were no significant differences in the number of recurrent HSL episodes between the LongoVital® and placebo groups (the median being 1.1 and 1.4 during the period 'days 121 to 180' and 0.9 and 0.8 during the period 'days 181 to 240', respectively; n = 52).

Secondary outcome 6. Duration of attack of recurrent HSL after use of the preventative intervention

During the post-treatment follow-up period, there were no significant differences in the median duration of recurrent HSL episodes between the LongoVital® and placebo groups (the median being 4.0 and 4.0 days during the period 'days 121 to 180' and 6.3 and 4.0 days during the period 'days 181 to 240', respectively; n = not reported).

Secondary outcome 7. Severity (lesion area, stage, pain) of attack of recurrent HSL after use of the preventative intervention

During the post-treatment follow-up period, there were no significant differences in the maximal size of recurrent HSL lesions between the LongoVital® and placebo groups (median = 2.9 and 5.0 mm during the period 'days 121 to 180' and 4.3 and 2.0 mm during the period 'days 181 to 240', respectively; n = not reported).

There were no relevant data for this intervention for our other outcomes.

Topical interventions

Topical aciclovir

Short-term (≤ 1 month) use

Two trials assessed the effects of short-term use of topical aciclovir 5% cream in preventing recurrence of HSL induced by sunlight or ultraviolet light (UVL) (Raborn 1997; Spruance 1991c). The Raborn 1997 trial assessed the effects of short-term use of topical aciclovir 5% cream starting 12 hours before sunlight exposure and continuing for 72 to 168 hours in preventing recurrence of HSL. The Spruance 1991c trial assessed the effects of short-term use of topical aciclovir 5% cream, beginning 5 minutes following experimental UVL exposure for 7 days. Please see Summary of findings 9 where we judged the quality of the evidence for this comparison as low to moderate for the following outcomes.

Primary outcome 1. Incidence of HSL during use of the preventative intervention

Neither of the 2 placebo-controlled trials found significant differences in the recurrence of HSL between the aciclovir and placebo groups nor did the meta-analysis of the 2 trials (pooled RR 0.91, 95% CI 0.48 to 1.72; n = 271; I^2 statistic = 66%; 2 trials; see Analysis 9.1).

Primary outcome 2. Adverse effects during use of the preventative intervention

Only the Raborn 1997 trial assessed the adverse events and found no differences between the 2 groups (RR 1.17, 95% CI 0.59 to 2.32; n = 191; see Analysis 9.2).

Secondary outcome 1. Duration of attack of recurrent HSL during use of the preventative intervention

Only the Spruance 1991c trial assessed this outcome and found no differences in the mean healing time to normal skin (6.8 days versus 7.4 days; P = 0.70; n = 52).

Secondary outcome 2. Severity (lesion area, stage, pain) of attack of recurrent HSL during use of the preventative intervention

Only the Spruance 1991c trial assessed the severity of recurrent HSL and found no differences in aborted lesions (RR 1.02, 95% CI 0.19 to 5.57; n = 52; see Analysis 9.3), mean maximal lesion area (110 mm^2 versus 72 mm^2; P = 0.88; n = 52), and mean duration of pain (3.7 days versus 3.6 days; P > 0.10; n = 52).

Secondary outcome 5. Incidence of HSL after use of the preventative intervention

The Raborn 1997 trial also assessed the recurrences of HSL in a 4-day post-treatment follow-up period and found fewer recurrences of HSL in the aciclovir group (RR 0.35, 95% CI 0.13 to 0.94; n = 181; Analysis 9.4).

There were no relevant data for this intervention for our other outcomes.

Topical aciclovir 5% plus 348U87 3%

Short-term (≤ 1 month) use

A placebo-controlled trial evaluated the effects of short-term use of topical aciclovir 5% plus 348U87 3% (a ribonucleotide reductase inhibitor) cream, starting immediately after UVL exposure and continuing for 7 days (Bernstein 1994). Please see Summary of findings 10 where we judged the quality of the evidence for this comparison as very low for the following outcomes.

Primary outcome 1. Incidence of HSL during use of the preventative intervention

There were no significant differences in the development of HSV(+) lesions (RR 0.78, 95% CI 0.19 to 3.14; n = 51; Analysis 10.1) and development of lesions consistent with HSL (RR 1.46, 95% CI 0.53 to 3.99; n = 51; see Analysis 10.2) between the 2 groups.

Secondary outcome 1. Duration of attack of recurrent HSL during use of the preventative intervention

There were no significant differences in the healing time (MD 2.50 days, 95% CI -1.39 to 6.39; n = 9; see Analysis 10.3) between the 2 groups.

Secondary outcome 2. Severity (lesion area, stage, pain) of attack of recurrent HSL during use of the preventative intervention

There were no significant differences in the maximal lesion size (MD 73.00 cm^2, 95% CI -42.22 to 188.22; n = 9; see Analysis 10.4) between the 2 groups.

There were no relevant data for the comparison of these interventions for our other outcomes.

Long-term (> 1 month) use

A placebo-controlled cross-over trial, Gibson 1986, evaluated the efficacy of aciclovir cream applied to all previously affected areas 4 times per day for 16 weeks.

Primary outcome 1. Incidence of HSL during use of the preventative intervention

The trial found significantly fewer research-diagnosed recurrences of HSL during a 16-week period when on aciclovir cream treatment than on placebo (the mean being 0.5 and 1.1, respectively; standard deviation (SD) not reported; P < 0.05 calculated by trialists; n = 23). However, no significant differences existed in the mean number of participant-reported recurrences between aciclovir cream treatment and placebo (the mean being 1.6 and 2.4, respectively; SD not reported; P ≥ 0.05 calculated by trialists; n = 23).

Primary outcome 2. Adverse effects during use of the preventative intervention

There were no significant adverse events while on either aciclovir cream or placebo (n = 23).

Secondary outcome 1. Duration of attack of recurrent HSL during use of the preventative intervention

The trial found significantly fewer mean days with HSL present when on aciclovir cream treatment than on placebo (the mean being 9.5 and 12.4 days, respectively; SD not reported; P < 0.01 calculated by trialists). Also, the trial found significantly fewer mean days with any symptom or sign of HSL present when on aciclovir cream treatment than on placebo (the mean being 12.2 and 17.4 days, respectively; SD not reported; P < 0.001 calculated by trialists).

There were no relevant data for this intervention for our other outcomes.

Foscarnet

A placebo-controlled trial, Bernstein 1997, examined the effects of topical application of foscarnet 3% cream 8 times daily (at least every 2 hours while awake) for 7 days in preventing experimental UVL-induced HSL. Please see Summary of findings 11 where we judged the quality of the evidence for this comparison as moderate for the following outcomes.

Primary outcome 1. Incidence of HSL during use of the preventative intervention

There were no significant differences in the researcher-diagnosed recurrence of HSL (RR 1.08, 95% CI 0.82 to 1.40; n = 295; see Analysis 11.1) between the foscarnet and placebo groups.

Primary outcome 2. Adverse effects during use of the preventative intervention

No significant differences were found in adverse events either leading to withdrawals (RR 2.96, 95% CI 0.12 to 72.11; n = 302; see Analysis 11.2) or application site reactions (RR 2.47, 95% CI 0.79 to 7.69; n = 302; see Analysis 11.3) between the foscarnet and placebo groups.

Secondary outcome 1. Duration of attack of recurrent HSL during use of the preventative intervention

The healing time did not significantly differ between the foscarnet and placebo groups (MD -0.21 days, 95% CI -1.68 to 1.26; n = 125; see Analysis 11.4).

Secondary outcome 2. Severity (lesion area, stage, pain) of attack of recurrent HSL during use of the preventative intervention

There were no significant differences in the mean lesion area (MD -16.00, 95% CI -38.96 to 6.96; n = 124; see Analysis 11.5), maximum lesion area (MD -30.00, 95% CI -72.64 to 12.64; n = 124; see Analysis 11.6), and duration of pain (MD 0.10, 95% CI -1.11 to 1.31; n = 113; see Analysis 11.7) between the foscarnet and placebo groups.

There were no relevant data for this intervention for our other outcomes.

1,5-pentanediol

A placebo-controlled trial evaluated the effects of twice daily application of topical 1,5-pentanediol (PD) gel for 26 weeks in preventing HSL (Busch 2009). Please see Summary of findings 12 where we judged the quality of the evidence for this comparison as moderate to low for the following outcomes.

Primary outcome 1. Incidence of HSL during use of the preventative intervention

The trial found no significant differences in the number of recurrences between the PD and placebo groups (109 episodes out of 50 participants versus 120 episodes out of 52 participants; P > 0.05 calculated using the Mann-Whitney test by trialists; n = 102).

Primary outcome 2. Adverse effects during use of the preventative intervention

No adverse events leading to discontinuation were observed in either group (n = 102).

Secondary outcome 2. Severity (lesion area, stage, pain) of attack of recurrent HSL during use of the preventative intervention

There were no significant differences in the severity of attack of recurrent HSL between the 2 groups (RR 1.05, 95% CI 0.91 to 1.20; episodes = 224; see Analysis 12.1).

There were no relevant data for this intervention for our other outcomes.

2-hydroxypropyl-β-cyclo dextrin

A placebo-controlled trial, Senti 2013, examined the effects of twice daily application of topical 2-hydroxypropyl-β-cyclo dextrin (2-HPβCD) 20% gel for 6 months in preventing HSL.

Primary outcome 1. Incidence of HSL during use of the preventative intervention

The trialists did not provide the exact numerical data on recurrences but presented them in plots. The 2-HPβCD group had significantly more recurrences than the placebo group (P = 0.003 calculated using the Mann-Whitney test by the trialists; n = 33). Both groups had significantly fewer recurrences during than before the study (P < 0.001 calculated by the trialists; n = 33).

Secondary outcome 1. Duration of attack of recurrent HSL during use of the preventative intervention

There were no differences in the duration of the relapses between the 2-HPβCD and placebo groups.

Secondary outcome 2. Severity (lesion area, stage, pain) of attack of recurrent HSL during use of the preventative intervention

There were no differences in the maximal size of the relapses between the 2-HPβCD and placebo groups. Although the 2-HPβCD group experienced less pain than the placebo group, the cumulative burden of pain assessed using the area-under-curve (AUC) of the daily pain visual analogue scale level was not significantly different between the 2 groups (P = 0.101). However, the symptoms were more severe in the placebo than in the 2-HPβCD group: the symptom scores were significantly higher in the former group for tingling (P = 0.040), burning (P = 0.028), and total symptoms (P = 0.048), but not for tension (P = 0.156), hypersensitivity (P = 0.119), and itching (P = 0.283).

There were no relevant data for this intervention for our other outcomes.

Sunscreen

A total of three placebo-controlled trials assessed the efficacy of sunscreen in preventing HSL, with one parallel trial using solar radiation, Mills 1987, and two cross-over trials using experimental UVL (Duteil 1998; Rooney 1991). Please see Summary of findings 13 where we judged the quality of the evidence for this comparison as low to very low for the following outcomes.

Primary outcome 1. Incidence of HSL during use of the preventative intervention

As shown in Analysis 13.1, application of sunscreen did not reduce the recurrences of HSL induced by sunlight (RR 1.13, 95% CI 0.25 to 5.06; n = 51; 1 trial), but significantly reduced the clinically diagnosed recurrences induced by experimental UVL (pooled RR 0.07, 95% CI 0.01 to 0.33; n = 111; I^2 statistic = 0%; 2 trials; number needed to treat to benefit (NNTB) = 3; 95% CI 2 to 4). The Rooney 1991 trial found sunscreen use significantly reduced virologically confirmed recurrences of HSL (RR 0.04, 95% CI 0.01 to 0.30; n = 73; 1 trial; NNTB = 2; 95% CI 2 to 3; see Analysis 13.2).

There were no relevant data for this intervention for our other outcomes.

Interventions given by injection

Three immunomodulating treatments were given by injection (interferon (Ho 1984; Pazin 1979), intradermal gamma globulin (Redman 1986), and thymopentin (Bolla 1985)).

Interferon

A placebo-controlled trial, Ho 1984, investigated whether either presurgical or postsurgical intramuscular administration of interferon (3 and 7 doses of 3.5 x 10^4 units/kg of body weight, respectively) could reduce recurrences of HSL in participants receiving microvascular decompression for trigeminal neuralgia. Another placebo-controlled trial, Pazin 1979, evaluated the effects of interferon administered intramuscularly for 5 days (10 doses of 3.5 x 10^4 units/kg of body weight), beginning on the day before receiving the same surgical procedure. Please see Summary of findings 14 where we judged the quality of the evidence for this comparison as very low to moderate for the following outcomes.

Primary outcome 1. Incidence of HSL during use of the preventative intervention

When assessing recurrences of HSL defined by the presence of clinical lesions, isolation of virus, or both (Analysis 14.1), the presurgical group was associated with a significant increase in recurrences (RR 1.59, 95% CI 1.05 to 2.41; n = 32), but no significant differences were found between the postsurgical and placebo groups (RR 0.99, 95% CI 0.59 to 1.66; n = 44). On the other hand, continuous pre- and postsurgical administration of interferon was associated with a significant decrease in the recurrences of HSL (RR 0.57, 95% CI 0.34 to 0.95; n = 37).

Primary outcome 2. Adverse effects during use of the preventative intervention

A significant increase in adverse events presenting as fever was found across the 3 interferon groups when compared with placebo (pooled RR 2.30, 95% CI 1.44 to 3.67; I^2 statistic = 0%; n = 114; 3 trials; see Analysis 14.2). One trial, Pazin 1979, found no significant differences in other adverse events including pain and tenderness at injection site (RR 0.95, 95% CI 0.06 to 14.04), malaise, nausea, or vomiting (RR 1.74, 95% CI 0.81 to 3.70) between the interferon and placebo groups (n = 37; see Analysis 14.3).

Secondary outcome 2. Severity (lesion area, stage, pain) of attack of recurrent HSL during use of the preventative intervention

In the Ho 1984 trial, the mean lesion area was 26, 135, and 30 mm^2 for the presurgical, postsurgical, and placebo groups, respectively (the trials did not report the SDs but stated no differences between them). The Pazin 1979 trial found no significant difference in the mean lesion area between the interferon and placebo groups (0.7 and 4.0 cm^2, respectively; SD not reported; P > 0.05 calculated by trialists).

There were no relevant data for this intervention for our other outcomes.

Gamma globulin

The Redman 1986 trial assessed the efficacy of intradermal administration of gamma globulin in preventing recurrence of HSL in a six-month follow-up period. Please see Summary of findings 15 where we judged the quality of the evidence for this comparison as low for the following outcomes.

Primary outcome 1. Incidence of HSL during use of the preventative intervention

The gamma globulin and control groups did not significantly differ in the mean number of herpes lesions (2.65 and 2.76 days, respectively; SD not reported; no significant differences calculated by the trialists; n = 84).

Secondary outcome 1. Duration of attack of recurrent HSL during use of the preventative intervention

The gamma globulin and control groups did not significantly differ in the mean number of days to vesicle healing (MD 0.70 days, 95% CI -0.55 to 1.95; n = 72; see Analysis 15.1).

Secondary outcome 2. Severity (lesion area, stage, pain) of attack of recurrent HSL during use of the preventative intervention

The gamma globulin and control groups did not significantly differ when 'less severe recurrences than usual' were measured (RR 0.97, 95% CI 0.74 to 1.28; n = 73; see Analysis 15.2).

There were no relevant data for this intervention for our other outcomes.

Thymopentin

A placebo-controlled trial, Bolla 1985, evaluated the effects of 6 weeks of treatment with subcutaneous administration of thymopentin in preventing recurrence of HSL in a 18-week follow-up period. Please see Summary of findings 16 where we judged the quality of the evidence for this comparison as moderate for the following outcomes.

Primary outcome 1. Incidence of HSL during use of the preventative intervention

During the follow-up period, the incidence of recurrent HSL was lower in the thymopentin group than the placebo group (median = 0.2 (range = 0.0 to 2.7) and 0.9 (range = 0.1 to 2.0) relapses/month, respectively; P = 0.0027 using the Mann-Whitney test by trialists; n = 36).

Primary outcome 2. Adverse effects during use of the preventative intervention

The 2 groups did not significantly differ in adverse events (RR 2.00, 95% CI 0.42 to 9.58; n = 36; see Analysis 16.1).

There were no relevant data for this intervention for our secondary outcomes.

Interventions given by vaccination

HSV vaccine

A placebo-controlled trial, Altmeyer 1991, tested the efficacy of a HSV type I subunit vaccine in preventing recurrences of HSL. Please see Summary of findings 17 where we judged the quality of the evidence for this comparison as moderate for the following outcomes.

Primary outcome 1. Incidence of HSL during use of the preventative intervention

The vaccine and placebo groups did not differ in the mean number of recurrences (1.6 versus 1.3 recurrences in a 4-month period; P = 0.10 calculated by trialists; n = 58). Both groups had a significantly fewer number of recurrences when compared with baseline (vaccine group: from 2.2 to 1.6, P < 0.01 calculated by trialists; placebo group: from 2.6 to 1.3, P < 0.001 calculated by the trialists; n = 58).

Primary outcome 2. Adverse effects during use of the preventative intervention

The vaccine and placebo groups had 22 and 13 adverse events per 100 injections. (Several adverse events might have occurred in the same participant; the trialists conducted no statistical tests.)

There were no relevant data for this intervention for our secondary outcomes.

Yellow fever vaccination

A placebo-controlled trial, Møller 1997, examined the efficacy of yellow fever vaccination in preventing recurrences of HSL in a 12-month follow-up period. Please see Summary of findings 18 where we judged the quality of the evidence for this comparison as moderate for the following outcomes.

Primary outcome 1. Incidence of HSL during use of the preventative intervention

The vaccine and placebo groups did not significantly differ in the mean number of recurrences (5 and 7, respectively; SD and P values not reported; n = 24) and the median number of recurrences (both being 5.5; P values not reported; n = 24).

Primary outcome 2. Adverse effects during use of the preventative intervention

The vaccine and placebo groups did not differ significantly in the number of participants with adverse events (RR 0.33, 95% CI 0.01 to 7.45; n = 24; see Analysis 17.1).

There were no relevant data for this intervention for our secondary outcomes.

Laser

Please see Summary of findings 19 where we judged the quality of the evidence for these comparisons as low to very low for the following outcomes.

Low-energy gallium-aluminium-arsenide laser

The de Carvalho 2010 trial evaluated the efficacy of a 10-week low-energy gallium-aluminium-arsenide laser phototherapy (3 to 4.5 J/cm^2) in preventing recurrence of HSL during a 16-month follow-up period.

Primary outcome 1. Incidence of HSL during use of the preventative intervention

The number of recurrences per month did not differ significantly between the laser and control groups (0.076 and 0.116, respectively; P = 0.076 calculated using the Mann-Whitney U test by the trialists; n = 71).

Primary outcome 2. Adverse effects during use of the preventative intervention

No adverse events were observed in either group (n = 71).

Secondary outcome 2. Severity (lesion area, stage, pain) of attack of recurrent HSL during use of the preventative intervention

The monthly average lesion size was significantly smaller in the laser group than in the control group (0.122 and 0.223 mm, respectively; P = 0.013 calculated using the Mann-Whitney U test by the trialists; n = 71). The inflammatory oedema was significantly less in the laser group than in the control group (the monthly mean being 0.015 and 0.00196, respectively; P = 0.031 calculated using the Mann-Whitney U test by the trialists; n = 71). There were no significant differences in the pain levels between the 2 groups (the monthly mean being 0.113 and 0.184; P = 0.051 calculated using the Mann-Whitney U test by the trialists; n = 71).

There were no relevant data for this intervention for our other outcomes.

Low-intensity diode laser therapy

The Schindl 1999 trial tested the effects of a 2-week low-intensity diode laser therapy (48 J/cm^2) in preventing recurrence of HSL during a 52-week follow-up period. A significantly longer median recurrence-free interval was found in the laser group (37.5 weeks; range = 2 to 52 weeks) than in the control group (3 weeks; range = 1 to 20 weeks) (P < 0.0001 calculated using the Wilcoxon rank-sum test by trialists; MD 30.00, 95% CI 21.42 to 38.58; n = 48; see Analysis 18.1), although this measure was not a prespecified outcome in our protocol.

Primary outcome 2. Adverse effects during use of the preventative intervention

No adverse events were observed in either group (n = 48).

There were no relevant data for this intervention for our other outcomes.

Hypnotherapy

The Pfitzer 2005 trial assessed the efficacy of five weekly hypnotherapy sessions in preventing recurrence of HSL during a follow-up period of six months in comparison with no hypnotherapy (control). Please see Summary of findings 20 where we judged the quality of the evidence for this comparison as very low for the following outcomes.

Primary outcome 1. Incidence of HSL during use of the preventative intervention

The frequency of recurrences significantly decreased in the hypnotherapy group (from 10.4 ± 7.6 to 5.2 ± 3.3; MD -5.20, 95% CI -10.34 to -0.06), but did not change in the control group (from 7.2 ± 5.7 to 8.5 ± 6.8; MD 1.30, 95% CI -3.94 to 6.54) (mean change in frequency of recurrences: MD -6.50, 95% CI -8.76 to -4.24; n = 21; see Analysis 19.1).

Secondary outcome 2. Severity (lesion area, stage, pain) of attack of recurrent HSL during use of the preventative intervention

The intensity of symptoms significantly diminished in the hypnotherapy group (from 26.0 ± 10.3 to 15.0 ± 7.0; MD -11.00, 95% CI -18.72 to -3.28), while that of the control group did not change significantly (from 24.4 ± 6.1 to 23.1 ± 3.8; MD -1.30, 95% CI -5.55 to 2.95) (mean change in the intensity of symptoms: MD -9.70, 95% CI -12.46 to -6.94; n = 21; see Analysis 19.2). The levels of pain did not change significantly in either the hypnotherapy group (MD -2.10, 95% CI -4.46 to 0.26) or the control group (MD 0.10, 95% CI -1.78 to 1.98). However, the levels of pain decreased significantly greater in the hypnotherapy group than in the control group (mean change in pain: MD -2.20, 95% CI -3.14 to -1.26; n = 21; see Analysis 19.2). The subjective impairment of appearance also improved significantly greater in the hypnotherapy group than in the control group (mean change in subjective impairment of appearance: MD -1.60, 95% CI -2.50 to -0.70; n = 21; see Analysis 19.2).

There were no relevant data for this intervention for our other outcomes.

DISCUSSION

Summary of main results

The evidence does not support the efficacy of short-term use of oral antiviral agents in preventing recurrence of herpes simplex labialis (HSL). The efficacy of short-term use of oral aciclovir in preventing recurrent HSL was inconsistent and lacked a dose-response relationship: 2 trials testing aciclovir 400 mg twice daily showed a reduced risk of recurrence of HSL (Schädelin 1988; Spruance 1988), while 1 trial testing aciclovir 800 mg twice daily, Raborn 1998, and 2 trials testing 200 mg 5 times daily, Spruance

1991a; Spruance 1991b, found no similar preventative effects. The direction of intervention effect was unrelated to the risk of bias of the studies. One trial, Miller 2004, found no preventative effect of short-term use of valaciclovir in reducing recurrence of HSL nor did a trial testing short-term use of famciclovir (Spruance 1999). On the other hand, long-term use of oral antiviral agents reduced the recurrence of HSL, but the clinical benefit was small. One trial found long-term use of oral aciclovir resulted in a small but significant reduction in either clinical or virological recurrence (by one episode per participant over a four-month period) (Rooney 1993). One trial found long-term use of valaciclovir effective in reducing the incidence of HSL (Baker 2003), but the clinical significance of the difference was very small, with a decrease of 0.09 episodes per participant per month. One trial, Gilbert 2007, found that when compared with an episodic regimen, a long-term suppressive regimen of valaciclovir had a lower incidence of HSL, but the difference was also very small, with a reduction of 0.10 episodes per participant per month.

One trial, Russell 1978, with a very high withdrawal rate (39.6% in the levamisole group and 15.7% in the placebo group) showed a reduced frequency of HSL in both the levamisole and placebo groups among those who completed the trial, but there were no significant differences between the 2 groups. Although the levamisole group was associated with a greater reduction in the frequency of HSL after taking into account the different baseline frequency of HSL (difference in means (MD) -2.00, 95% CI -2.24 to -1.76; see Analysis 7.1), the placebo group was associated with a greater reduction in the duration of attack of HSL (MD 0.70, 95% CI 0.22 to 1.18; see Analysis 7.3). Thus, there was no consistent evidence supporting the efficacy of levamisole in preventing HSL. Two other oral interventions, lysine and LongoVital® supplementation, did not prevent recurrence of HSL (Thein 1984; Pedersen 2001).

Similar to that for oral antiviral agents, the evidence shows no efficacy of short-term use of topical antiviral agents in preventing recurrent HSL. Two trials found no effects of short-term use of topical aciclovir 5% cream in preventing recurrence of HSL, Raborn 1997; Spruance 1991c, nor did another trial testing topical aciclovir 5% plus 348U87 3% cream (Bernstein 1994). One trial found no effects of short-term use of topical foscarnet 3% cream in preventing recurrent HSL (Bernstein 1997). The efficacy of long-term use of topical antiviral agents is uncertain. One trial, Gibson 1986, found long-term use of aciclovir cream significantly reduced research-diagnosed recurrences of HSL, but not participant-reported recurrences. Another trial found no effects of long-term use of topical 1,5-pentanediol gel in preventing HSL (Busch 2009). One study, Senti 2013, found participants who applied topical 2-hydroxypropyl-β-cyclo dextrin 20% gel had more recurrences than the placebo group, and the placebo group had milder symptoms of tingling and burning.

As shown in Analysis 13.1, application of sunscreen significantly prevented recurrent HSL induced by experimental ultraviolet light (UVL) (Duteil 1998; Rooney 1991), but did not reduce the recurrence of HSL induced by sunlight (Mills 1987). The efficacy of sunscreen under natural sunlight has not been confirmed.

The was a lack of consistent evidence supporting the efficacy of interferon in preventing recurrent HSL. Data from two trials, Ho 1984; Pazin 1979, showed an increased recurrence of HSL after presurgical administration of interferon, no difference in recurrence with postsurgical administration of interferon, but a decreased recurrence in those receiving continuous pre- and postsurgical administration of interferon. A trial, Redman 1986, found no efficacy of gamma globulin in preventing recurrent HSL, while another, Bolla 1985, found fewer incidences of recurrent HSL after six weeks of treatment with subcutaneous administration of thymopentin.

Both a HSV type I subunit vaccine and a yellow fever vaccine did not show a higher efficacy than placebo in preventing HSL (Altmeyer 1991; Møller 1997).

Two trials investigated the effects of low-level laser therapy in preventing recurrent HSL. One trial, de Carvalho 2010, found no difference in the number of recurrences and pain, but found a significantly smaller average lesion size (with a very small difference of 0.1 mm) and a significantly lower monthly average inflammatory oedema (with a tiny difference of 0.0046 on a '0 to 3' oedema score) in the laser group. Although the latter two measures were statistically significant, the differences between the laser and control groups did not appear to be clinically significant. The other trial, Schindl 1999, found a significantly longer median recurrence-free interval in the laser group (37.5 weeks versus 3 weeks in the control group), which was not a prespecified outcome in the present review.

One trial, Pfitzer 2005, found that hypnotherapy significantly reduced the frequency (MD -5.20, 95% CI -10.34 to -0.06 during a 6-month follow-up) and intensity of symptoms of HSL recurrences.

Overall completeness and applicability of evidence

The effects of oral and topical antiviral agents in preventing recurrent HSL have been extensively investigated. The body of evidence regarding oral and topical antiviral agents is adequate for us to conclude that long-term use of oral aciclovir and valaciclovir are effective in preventing recurrent HSL, while short-term use of either oral or topical antiviral agents is ineffective. On the other hand, there is a lack of evidence supporting the efficacy of long-term use of topical antiviral agents in preventing recurrent HSL.

The available body of evidence regarding other interventions is scanty, with only one or two trials for each intervention. There is no consistent evidence supporting the efficacy of levamisole and interferon in preventing HSL. The current limited evidence found no efficacy of lysine, LongoVital® supplementation, gamma globulin, HSV type I subunit vaccine, and yellow fever vaccine in preventing HSL. There is very limited evidence suggesting that thymopentin, low-level laser therapy, and hypnotherapy are effective in preventing HSL.

Quality of the evidence

Based on the following limitations, we rated the quality of the body of evidence low to moderate for most outcomes and very low for a few outcomes.

Limitations in the design and implementation of available studies suggesting high likelihood of bias

The risk of bias of the included trials varied from low to high (Figure 3). As shown in Figure 2, the high risk of bias most often appeared in the 'selective reporting' domain (12 (34%) out of 32 trials), followed by the 'other bias' domain (9 (28%) trials). The

cause for a high risk of bias in 'selective reporting' was either a lack of data on adverse events or details on efficacy outcomes. The causes for a high risk of 'other bias' included early stopping of the trial (Bernstein 1994), no washout period in cross-over trials (Gibson 1986; Gilbert 2007; Rooney 1993; Thein 1984), different baseline frequencies of HSL recurrences between the experimental and control groups (Pedersen 2001; Russell 1978), a low percentage of participants having a history of HSL (Schädelin 1988), and a lack of scheduled follow-ups (Schindl 1999).

Over half of the included trials (17/32) were published before 1996 when the reporting guidelines for randomised controlled trials (RCTs), the CONsolidated Standards Of Reporting Trials (CONSORT) Statement, was first proposed. These trials often did not provide detailed reports on the methods of random sequence generation, allocation concealment, blinding, and withdrawal or dropout.

In five included trials (Altmeyer 1991; Bolla 1985; Russell 1978; Senti 2013; Thein 1984), the incidence of HSL decreased in both the experimental and placebo groups, which may be attributed to either the placebo effect or an overestimation of the baseline incidence of HSL.

Indirectness of evidence (indirect population, intervention, control, outcomes)

Direct evaluation under natural sunlight exposure in the de Carvalho 2010 trial did not confirm the indirect evidence of the preventative efficacy of sunscreen use under experimental UVL in the Schindl 1999 trial.

Unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses)

As stated previously (Analysis 1.1), the preventative efficacy of short-term administration of oral aciclovir was inconsistent and lacked a dose-response relationship (see Summary of findings for the main comparison). Also, the efficacy of levamisole and interferon was inconsistent (see Summary of findings 7; Summary of findings 14). For other interventions, the direction of intervention effect was consistent.

Imprecision of results (wide confidence intervals)

For most interventions, there were only one or two relevant trials of limited sample size. We therefore downgraded the quality of evidence for imprecision.

High probability of publication bias

We were unable to detect publication bias because of the limited number of trials for each intervention.

Potential biases in the review process

We planned to conduct an intention-to-treat analysis by considering those with missing binary outcomes as treatment failures and carrying out a 'last observation carried forward' analysis for those with missing continuous or ordinal outcomes. However, many included trials did not report details of withdrawals or dropouts nor provided a participant flow chart (Bernstein 1994; Bolla 1985; de Carvalho 2010; Duteil 1998; Gibson 1986; Pfitzer 2005; Spruance 1991a; Spruance 1991b; Spruance 1991c; Thein 1984). We failed to conduct the planned analysis for missing data, and it is thus unclear whether the intervention effects were overestimated in these trials.

Agreements and disagreements with other studies or reviews

Three reviews, Opstelten 2008; Worrall 2009; Rahimi 2012, were published before we conducted this review, with Rahimi 2012 limited to antiviral agents and having a four-year gap between the year of literature search and publication. They included RCTs from searching various databases up to April 2008, February 2009, and 2008, respectively. Two reviews, Opstelten 2008; Worrall 2009, found in line with our review that long-term use of oral antiviral agents are effective in preventing HSL and found mixed results regarding the preventative efficacy of sunscreens.

The Opstelten 2008 review regarded short-term use of topical antiviral agents effective in preventing HSL and interpreted Raborn 1997 as showing the efficacy of topical aciclovir cream in preventing HSL. However, in the Raborn 1997 trial, the proportion of participants presenting with recurrent HSL did not significantly differ between the aciclovir and placebo groups (15/91 versus 23/90). Only in the 'treatment period plus four days' follow-up period' did the proportion of participants having recurrent HSL differ significantly between the two groups. The abstract of the Opstelten 2008 review stated short-term use of oral antiviral agents would provide some protection against recurrent HSL, although its main text reported the inconsistent results from the Raborn 1998; Spruance 1988; Spruance 1991a; and Spruance 1991b trials.

The Worrall 2009 review could not conclude whether topical antiviral agents are effective in preventing HSL based on results from 2 trials on aciclovir 5% cream (Raborn 1997; Spruance 1991c). Our review included 2 more trials on aciclovir 5% plus 348U87 3% cream, Bernstein 1994, and foscarnet 3% cream, Bernstein 1997, and found no effects of short-term use of topical antiviral agents in preventing recurrent HSL.

The Rahimi 2012 review was in agreement with us that topical aciclovir cream did not appear effective in preventing HSL. The Rahimi 2012 review examined the effects of various antivirals and found oral aciclovir and valaciclovir, but not famciclovir, effective in preventing HSL. However, the Rahimi 2012 review did not take into consideration the length of antiviral use.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence indicates that long-term use of oral antiviral agents reduces the recurrence of herpes simplex labialis (HSL). There is very limited evidence suggesting that thymopentin, low-level laser therapy, and hypnotherapy are effective in preventing recurrent HSL. The efficacy of long-term use of topical aciclovir cream is uncertain. The preventative efficacy of sunscreen under realistic natural sunlight conditions has not been confirmed.

On the other hand, the current evidence found no preventative effects of short-term use of oral or topical antiviral agents, lysine, LongoVital® supplementation, gamma globulin, HSV type I subunit vaccine, and yellow fever vaccine. Also, there is no consistent evidence supporting the efficacy of levamisole and interferon in preventing HSL.

Implications for research

Although the Rooney 1993 trial found long-term use of oral aciclovir 400 mg twice daily effective in preventing HSL, the long-term safety was unclear. It is also unknown if long-term use of a smaller dosage of oral aciclovir is effective in preventing recurrent HSL. The current evidence regarding long-term use of topical antiviral agents, thymopentin, low-level laser therapy, and hypnotherapy is very limited. Further trials on these interventions are required to fill in the gap in knowledge. There is only one small randomised controlled trial (RCT) examining the effects of sunscreens in preventing HSL induced by sunlight. Thus, there is a call for large RCTs of adequate use of high-SPF (sun protection factor) sunscreens for preventing HSL under realistic natural sunlight conditions.

Furthermore, we found that measured outcomes varied widely across the included trials, which resulted in difficulty in completing the present review. It is desirable to define a set of core outcomes for studies on the interventions for prevention of HSL, and all future trials should measure and report these core outcomes. Before such a set of core outcomes is defined, we suggest trialists measure and report the outcomes of interest in the present review (see Types of outcome measures).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Altmeyer 1991

Methods	This was a multicentre, randomised, double-blind study
Participants	**Inclusion criteria** • Detection of herpes simplex virus type I in the herpes lesions • Occurrence of at least 4 episodes of herpes eruptions within the last 4 months before the start of the study • A herpes episode or a recurrence of herpes had to meet the following clinical criteria: small grouped vesicles on gerö-coated background with discomfort, such as burning or stinging **Exclusion criteria** • Had acute or chronic infections needing therapy, malignancies, and disease associated with immunosuppression • Age under 18 years and over 50 years • Application of antivirals after the start of the study • Pregnancy A total of 64 participants were randomised, with 35 in the vaccine group and 29 in the placebo group
Interventions	• A: HSV type I subunit vaccine • B: placebo The participants were followed up for a 4-month 'pilot phase' without treatments. Then in the first main phase of 4 months' duration, the assigned treatment was given weekly for 3 times on days 120, 127, and 134. In the second main phase of another 4 months' duration, the assigned treatment was repeated for another 3 times on days 240, 247, and 254
Outcomes	1. Number of HSL recurrences in the first main phase and the total main phase (compared with that in the pilot phase) 2. Adverse events
Notes	Setting: university hospitals Country: Germany Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The methods of random sequence generation were not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The vaccine and placebo preparations were identical in appearance and labelling except for the consecutive number of the labelling

Altmeyer 1991 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	The vaccine and placebo preparations were identical in appearance and labelling except for the consecutive number of the labelling
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1 participant dropped out immediately after allocation to the vaccine group. 1 participant in the vaccine group and 1 in the placebo group withdrew before treatments started. 1 in the vaccine group withdrew after completing the vaccination due to an adverse event. 1 in the vaccine group and 1 in the placebo group withdrew in the second main phase. Thus, a total of 4 (11.4%) and 2 (6.9%) participants in the vaccine and placebo group, respectively, did not complete the study
Selective reporting (reporting bias)	Low risk	Both efficacy and adverse outcomes were reported
Other bias	Unclear risk	There was insufficient information to assess whether an important risk of bias existed

Baker 2003

Methods	This was a pooled analysis of 2 randomised, double-blind, placebo-controlled, single-centre studies
Participants	**Inclusion criteria** • Men or women aged 18 years or older who tested seropositive for herpes simplex virus type 1 by Western blot test and had a history of at least 4 herpes simplex virus type 1 herpes labialis lesions in the previous year **Exclusion criteria** • People were excluded if they (1) had used any antiherpes medication in the month prior to enrolment; (2) showed evidence of active herpes labialis reactivation; (3) were immunosuppressed or taking immunosuppressant medication; or (4) were women who were breast-feeding or had a positive pregnancy test A total of 98 participants were randomised, with 49 in each group
Interventions	• A: oral valaciclovir 500 mg once daily for 4 months • B: oral placebo once daily for 4 months If there was clinical evidence of recurrent herpes labialis, participants received open-label oral valaciclovir 500 mg twice daily for 5 days. Participants resumed their assigned study medication at the end of the 5-day open-label regimen
Outcomes	1. Incidence of HSL during use of the preventative intervention (researcher-diagnosed): participants were instructed to contact their clinician within 8 hours of any sign of a recurrence of a herpes labialis lesion occurring at any time during the 4-month treatment period. Participants were to be examined at the clinic within 12 hours of onset of a suspected recurrent lesion 2. Adverse effects during use of the preventative intervention
Notes	Setting: a university hospital Country: US Funding source: supported in part by GlaxoSmithKline
Risk of bias	

Baker 2003 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The methods of random sequence generation were not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All patients randomized to treatment who attended at least 1 of the monthly clinic visits were included in the efficacy analyses." "Two patients (1 in the valaciclovir group and 1 in the placebo group) who were lost to follow-up and 1 patient in the valaciclovir group who withdrew prior to the first clinic visit were not included in the efficacy analyses" Comment: only 3 (3.1%) out of 98 participants were lost to follow up
Selective reporting (reporting bias)	Low risk	The number of participants with recurrences, number of recurrences per participant per month, and incidence of adverse events during the treatment period were reported
Other bias	Unclear risk	There was insufficient information to assess whether an important risk of bias existed

Bernstein 1994

Methods	This was a double-blind, randomised, placebo-controlled trial
Participants	**Inclusion criteria** • Healthy adults with a history of sunlight-induced herpes labialis and at least 2 episodes of herpes labialis in the preceding year **Exclusion criteria** • Use of anti-inflammatory medication within 1 week was not permitted • Use of immunomodulatory drugs or antiviral mediation within 30 days was not permitted • Use of lip balm, cosmetics, soaps, fragrances, or medication known to produce abnormal response to sunlight were also prohibited A total of 51 participants were randomised, with 25 and 26 in the aciclovir and 348U87 group and placebo group, respectively
Interventions	• A: topical aciclovir and 348U87 cream (consisted of aciclovir 5% and 348U87 3% in a 40% propylene glycol base) • B: placebo cream Immediately after UV exposure, participants began treatment by application of the study medication to the UV-exposed quadrant. The cream was applied every 2 hours while awake (maximum 8 applica-

Bernstein 1994 *(Continued)*

	tions/day), for 7 days. If herpetic lesions developed, treatment was continued until the lesions healed up to a maximum of 5 additional days
Outcomes	1. Incidence of HSL during use of the preventative intervention (researcher-diagnosed): number of participants developing HSV culture-positive or any lesions consistent with herpes labialis 2. Severity of attack of recurrent HSL during use of the preventative intervention: number of HSV culture-positive lesions and number of lesions consistent with herpes labialis
Notes	Setting: research institutes (James N. Gamble Institute of Medical Research and Hilltop Research) Country: US Funding source: Burroughs Wellcome & Co.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomly assigned according to a code supplied by the sponsor" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "A subsequent double blind evaluation was performed...on 51 subjects to assess the effects of a combination of topical aciclovir and 348U87 compared to placebo on lesion development and severity"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "A subsequent double blind evaluation was performed...on 51 subjects to assess the effects of a combination of topical aciclovir and 348U87 compared to placebo on lesion development and severity"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No dropouts or withdrawals were reported
Selective reporting (reporting bias)	High risk	The adverse effects during use of the preventative intervention were not reported
Other bias	High risk	Quote: "The sample size for the drug evaluation was estimated to be 50 patients per group to achieve a power of 80% and a significance level of 0.05 if the drug decreased recurrences by 60%. An interim analysis after 50 subjects was planned." "Because there was no trend for the benefit of the drug treatment the study was discontinued after the interim analyses" Comment: this was an early-stopped trial. Therefore, a small benefit of the study drug could not be ruled out

Bernstein 1997

Methods	This was a randomised, double-blind, multicentre trial
Participants	**Inclusion criteria** • Healthy adults with a history of sunlight-induced herpes labialis

Bernstein 1997 *(Continued)*

	Exclusion criteria • None reported A total of 310 participants were enrolled at the 4 centres, but 8 did not receive the study drug. Of the 302 treated participants, 152 received foscarnet 3% and 150 received placebo cream. 7 participants (4 for foscarnet and 3 for placebo) were excluded from the efficacy analysis because of major predefined protocol violations
Interventions	• A: topical foscarnet 3% (trisodium phosphonoformate) in an oil-in-water cream • B: vehicle alone Beginning immediately after ultraviolet radiation (UVR) exposure of the lips, participants applied the cream on the UVR-exposed area and surrounding skin 8 times daily (at least every 2 hours while awake) for 7 days, but if a herpetic lesion developed, dosing was extended as necessary to treat the lesion for at least 4 days. The time of each application was recorded in a participant diary
Outcomes	1. Recurrence of HSL (researcher-diagnosed): following UVR exposure of the lips, participants returned on days 2, 3, 5, 8 ± 1, and 14 ± 1 and were examined for the development of herpes labialis 2. Adverse events 3. Healing time (from appearance of vesicle to loss of crust) 4. Mean lesion area 5. Maximum lesion area 6. Duration of pain
Notes	Setting: 4 medical centres Country: US Funding source: Astra Arcus AB, Sweden

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The methods of randomisation were not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "This was a randomized, double-blind investigation" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "This was a randomized, double-blind investigation" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "A total of 310 subjects were enrolled at the four centers, but 8 did not receive the study drug." "Seven subjects (four for foscarnet and three for placebo) were excluded from the efficacy analysis because of major predefined protocol violations" Comment: there were 15 (4.8%) dropouts/withdrawals out of 310 enrolled participants

Bernstein 1997 *(Continued)*

Selective reporting (reporting bias)	Low risk	The efficacy outcomes and adverse effects were reported
Other bias	Unclear risk	There was insufficient information to assess whether an important risk of bias existed

Bolla 1985

Methods	This was a placebo-controlled, double-blind, randomised, multicentre study
Participants	**Inclusion criteria** • Frequent recurrences of herpes infections (on average not less than 12 per year, i.e., 1 per month) • Viral culture was desired but not obligatory • Duration of the disease should have been longer than 6 months **Exclusion criteria** • People with significant renal, haematologic, hepatic, or other acute/chronic disease (severe congestive heart failure, uncontrolled diabetes mellitus, etc.) that might have jeopardised their ability to participate in the study were excluded, as well as females with childbearing potential using no adequate contraception A total of 36 participants older than 16 years and suffering from frequent recurrences (≥ 12 relapses/year) of herpes labialis infections, with 18 in each group, entered this study
Interventions	• A: thymopentin • B: placebo Thymopentin was provided in a concentration of 100 mg/ml. A 6-week treatment with 0.5 ml of the test drug (50 mg thymopentin or placebo), administered by the subcutaneous route 3 times weekly, was performed
Outcomes	After the double-blind course of treatment, a follow-up period of 18 weeks without any treatment was proposed. After 6 weeks' treatment and at the end of the follow-up period, the outcomes below were assessed: 1. Incidence of herpes labialis after use of the preventative intervention 2. Adverse effects during use of the preventative intervention 3. Duration of attack of herpes labialis after use of the preventative intervention
Notes	Setting: 14 medical centres Country: Europe Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The methods of randomisation were not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned

Bolla 1985 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Thymopentin and placebo (vehicle) were supplied in coded, unidentifiable 5-ml multidose vials"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No dropouts or withdrawals were reported
Selective reporting (reporting bias)	Low risk	Both the efficacy outcomes and adverse effects were reported
Other bias	Unclear risk	There was insufficient information to permit judgement

Busch 2009

Methods	This was a randomised, double-blind, placebo-controlled trial
Participants	**Inclusion criteria** • Participants should have had at least 6 episodes of recurrent herpes during the preceding 12-month period **Exclusion criteria** • None reported A total of 105 participants were randomised to either 1,5-pentanediol (PD) (53 participants) or placebo (52 participants)
Interventions	• A: topical PD gel • B: placebo The clinical trial consisted of a prophylactic period of 26 weeks, during which at least 2 examinations (at the start of the trial and after 25 to 27 weeks) were performed. During the prophylactic phase, the participants applied PD or placebo gel twice daily to both lips. Upon occurrence of a herpes episode, the participant started immediately with the therapy phase and presented herself/himself promptly to the participating investigator for confirmation of the herpes symptoms. During the 5-day therapy phase, the gel was applied 8 times daily. On day 6 after the start of the therapy, the participant visited the investigator again for examination and evaluation of the healing process and started prophylactic treatment twice daily again until the next herpes episode
Outcomes	1. Incidence of HSL during use of the preventative intervention 2. Adverse effects during use of the preventative intervention 3. Severity (blistering, swelling, and pain) of attack of recurrent HSL during use of the preventative intervention
Notes	Setting: 4 study centres in Berlin Country: Germany Funding source: Natumin Pharma AB

Busch 2009 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization for this clinical trial was undertaken with the help of randomization plan NP/RL/060407/132"
Allocation concealment (selection bias)	Low risk	Quote: "The gel supplied to the patients had a consecutive random number on the label. This number was previously assigned to the PD gel and to the placebo gel externally. Neither the investigator nor the patients had any knowledge of what kind of treatment was given"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The PD and the placebo gel were packed in 4 g tubes and labelled for the clinical trial. The gels were not distinguishable by color or smell." "Neither the investigator nor the patients had any knowledge of what kind of treatment was given"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The gel supplied to the patients had a consecutive random number on the label. This number was previously assigned to the PD gel and to the placebo gel externally. Neither the investigator nor the patients had any knowledge of what kind of treatment was given." "The randomization code remained with the study sponsor until the final closure of the database"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of the 105 participants recruited, 3 (2.9%) participants who had been assigned to the PD group dropped out of the study
Selective reporting (reporting bias)	Low risk	The efficacy outcomes and adverse events were reported
Other bias	Unclear risk	There was insufficient information to permit judgement

de Carvalho 2010

Methods	This was a randomised controlled trial
Participants	**Inclusion criteria** • Young adults reporting recurring herpes labialis for at least 3 subsequent years, recruited from a university setting **Exclusion criteria** • Persons having previously undergone laser phototherapy or systemic aciclovir treatment and those presenting with herpes zoster were excluded as were persons presenting with the first symptoms of herpes labialis infection A total of 71 participants were randomly allocated to the experimental (laser) group (41 participants) and the control group (30 participants)
Interventions	• A: laser: 10 sessions (1 per week) of laser phototherapy (gallium-aluminium-arsenide (GaAlAs) laser; 780 nm; 60 mW; laser beam 0.04 cm^2; Twin Laser, MM Optics®, Brazil). The laser fluence used depended on the presence or not of HSV-1 infection: 4.5 J/cm^2 (3 s per point) for any stage of HSV-1 infection (prodromic stage, vesicles, or crusts); 3.0 J/cm^2 (2 s per point) otherwise. Laser phototherapy was applied punctually over the whole labial area, following 3 imaginary lines in each lip: the first in the transition to the dermis; the second, in the middle of the labial area, and the third, in the transition to the labial mucosa. Each line was composed of 10 points, 30 points per lip. If participants were subjected to

de Carvalho 2010 *(Continued)*

	the protocol of 3 J/cm^2, the total energy applied to the tissue per session was 7.2 J, and if participants were subjected to the protocol of 4.5 J/cm^2, the total energy applied to the tissue per session was 10.8 J. During the 10 weeks of laser phototherapy, the irradiation fluence could change, depending on the presence or not of HSV-1 infection (4.5 J/cm^2 or 3 J/cm^2) • B: control: no interventions, but participants were advised to apply topical aciclovir 5% 5 times a day if they showed HSV-1 infection at the beginning of the study period
Outcomes	1. Herpes labialis recurrences 2. Size of the lesions, scored as 0 for absent, 1 for small (0.1 to 2.0 mm), 2 for medium (2.1 to 5.0 mm), and 3 for large (larger than 5.0 mm) lesions 3. Presence of inflammatory oedema classified as 0 for absent, 1 for small (discrete swelling), 2 for medium (moderate swelling), and 3 for large (swelling covering a perimeter of 1 cm^2) 4. Intensity of pain on a 0 to 10 visual analogue scale
Notes	Setting: a university hospital Country: Brazil Funding source: non-profit organisations (Fundação de Amparo à Pesquisa do Estado de São Paulo, the Conselho Nacional de Desenvolvimento Científico e Tecnológico, and the Center of Research, Teaching and Clinics of Laser in Dentistry, School of Dentistry, University of São Paulo, Brazil)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Author's reply to our request: "Randomization was down [sic] through sortition"
Allocation concealment (selection bias)	Unclear risk	The authors replied to our request to say that no measures for allocation concealment were arranged
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was impossible because laser therapy was used in the experimental group without a corresponding sham treatment in the placebo group
Blinding of outcome assessment (detection bias) All outcomes	High risk	The authors replied to our request to say that the outcome assessors were the participant physicians
Incomplete outcome data (attrition bias) All outcomes	Low risk	The authors replied to our request to say that there was only 1 dropout
Selective reporting (reporting bias)	Low risk	Efficacy data were reported in the article. The authors replied to our request to say that they evaluated adverse events, but there were none detected
Other bias	Unclear risk	There was insufficient information to permit judgement

Duteil 1998

Methods	This was a randomised cross-over trial on preventing ultraviolet light-induced herpes labialis
Participants	**Inclusion criteria** • Adults who had a history of at least 2 herpes labialis recurrences per year

Duteil 1998 *(Continued)*

	Exclusion criteria • Presenting active herpes labialis A total of 19 participants were randomised to intervention A (9) and B (10)
Interventions	• A: sunblock stick in the first phase and vehicle stick in the second phase • B: vehicle stick in the first phase and sunblock stick in the second phase The very high protection sunblock stick (UVA and UVB) contained a photostable combination of Parsol® 1789, Eusolex® 6300, and Mexoryl™ SX (Laboratoires Galderma) The test product was applied (2 mg/cm^2) to the lips of the participant. 10 minutes after application of the product, half of the test zone (left or right, depending on where the last recurrence of herpes had occurred) was exposed to 4 times the participant's minimal erythema dose. Linen towels protected the remainder of the face and the neck. There was a 4-week washout period between the 2 phases
Outcomes	1. Incidence of HSL after use of the preventative intervention (number of participants with HSL recurrence after ultraviolet light)
Notes	Setting: a university hospital Country: France Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The methods of randomisation were not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding was not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding was not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No dropouts or withdrawals were mentioned
Selective reporting (reporting bias)	High risk	Only an efficacy outcome was reported
Other bias	Unclear risk	There was insufficient information to permit judgement

Gibson 1986

Methods	This was a randomised, double-blind, placebo-controlled, cross-over study

Gibson 1986 *(Continued)*

Participants	**Inclusion criteria** • People aged at least 16 years who had 6 or more recurrences per year of herpes labialis **Exclusion criteria** • None reported A total of 23 participants completed the trial
Interventions	• A: applied aciclovir cream for 16 weeks and then placebo cream for 16 weeks • B: applied placebo cream for 16 weeks and then aciclovir cream for 16 weeks The cream was applied to all previously affected areas 4 times per day. There was no washout period. The participants were subsequently observed for a further 16 weeks with no treatments
Outcomes	1. Number of participant-recorded recurrences 2. Number of doctor-confirmed recurrences 3. Time to first participant-recorded recurrence 4. Time to first doctor-confirmed recurrence 5. Number of days with lesions of herpes labialis present 6. Number of days with any sign or symptom of herpes labialis present 7. Adverse reactions during the use of the preventive intervention
Notes	Setting: 3 hospitals (London Hospital, Basildon Hospital, and Sant'Orsola Hospital) Country: UK and Italy Funding source: Wellcome Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The methods of randomisation were not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No dropouts or withdrawals were mentioned
Selective reporting (reporting bias)	Low risk	Efficacy outcomes and adverse events were reported
Other bias	High risk	There was no washout period. The outcome data of the first phase were unavailable

Gilbert 2007

Methods	This was a randomised, open-label, cross-over trial
Participants	**Inclusion criteria** • ≥ 18 years, had a history of at least 3 recurrent herpes labialis episodes in the previous year, and had a history of at least 50% of herpes labialis episodes with lesions that progressed according to the classification described by SL Spruance (prodrome, macule, papule, vesicle, ulcer, crust, healed) **Exclusion criteria** • Had a skin condition that affected the herpes area and might influence its course; had conditions likely to be associated with immunodeficiency or were taking immunosuppressive medication; allergy to aciclovir, valaciclovir, famciclovir, or ganciclovir or had ever had an infection with HSV-1 isolates resistant to these medications; was breastfeeding; had a positive pregnancy test at screening; or did not agree to practice contraception from initiation of study medication through 4 weeks after study completion or premature withdrawal from the study A total of 76 participants were randomised, received at least 1 dose of valaciclovir, and had at least 1 postbaseline evaluation (termed 'intention-to-treat exposed population' by the trialists). Of them, 60 participants had at least 1 postbaseline evaluation during each treatment period (termed 'cross-over population' by the trialists)
Interventions	• A: 'episodic regimen' (2 2 g doses of valaciclovir separated by 12 hours at first sign of prodrome) for 6 months, followed by 'suppressive regimen' (valaciclovir 1 g once daily) for 6 months • B: 'suppressive regimen' for 6 months, followed by 'episodic regimen' for 6 months Recurrences of HSL during the suppressive treatment were treated with episodic therapy
Outcomes	1. Number of recurrences of HSL 2. Median time to first recurrence in the first treatment period 3. Mean duration of recurrence 4. Size of lesions (mean and maximum total lesion area) 5. Mean severity of pain 6. Adverse events
Notes	Setting: a university hospital Country: US Funding source: GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The methods of randomisation were not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was impossible because of different regimens

Gilbert 2007 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding was impossible because of different regimens
Incomplete outcome data (attrition bias) All outcomes	High risk	16 (21%) out of 76 participants did not complete the study
Selective reporting (reporting bias)	Low risk	Efficacy and adverse outcomes were reported
Other bias	High risk	There was no washout period

Ho 1984

Methods	This was a randomised trial
Participants	**Inclusion criteria** • Patients admitted for their first microvascular decompression of the trigeminal sensory root with a positive history of herpes labialis **Exclusion criteria** • None reported A total of 55 participants were analysed
Interventions	• A: presurgical group: human leukocyte interferon (IFN), 3.5 x 10^4 units/kg of body weight, was administered intramuscularly in the morning and evening the day before surgery and once in the morning before surgery • B: postsurgical group: 7 doses of IFN were administered, beginning with 1 dose in the evening after surgery and 2 doses each day for 3 successive days • C: placebo group: equivalent volumes of human serum albumin, the IFN vehicle, were administered for 5 days beginning 1 day before surgery On days when the treatment groups did not receive IFN, they received placebo injections so that all 3 groups received 2 injections per day for 5 days
Outcomes	1. Number of participants with recurrence of HSL (diagnosed by presentation of herpes lesions, viral shedding, or both) 2. Adverse effects of IFN 3. Lesion area
Notes	Setting: a university hospital Country: US Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The methods of randomisation were not reported

Ho 1984 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind"; "all three groups received two injections per day for 5 days"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind"; "after data were collected on a total of 55 patients, the code was broken again and the results were analyzed"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	A total of 55 (85%) participants completed the study and were analysed. 10 other participants were enrolled and randomised but not evaluated: 5 were shedding HSV in the oropharynx before surgery, 2 refused treatment, and surgery was cancelled or postponed for 3 participants
Selective reporting (reporting bias)	Low risk	Both efficacy and adverse outcomes were reported
Other bias	Unclear risk	There was insufficient information to permit judgement

Miller 2004

Methods	This was a randomised, double-blind, placebo-controlled study
Participants	**Inclusion criteria** • HSV-seropositive people aged 12 years or older who were in good general health and scheduled to receive routine dental care, had a history of oral herpes simplex that recurred at least once per year, and had experienced at least 1 clinical recurrence within the previous year **Exclusion criteria** • People who were immunosuppressed or who were taking immunosuppressant medication, had liver or kidney dysfunction, were pregnant, who were HSV-seronegative, or had clinical evidence of an active oral HSV lesion at the beginning of the study A total of 150 participants were enrolled in the trial. 23 participants who failed to return to the clinic and 2 participants who were HSV-seronegative were excluded from analysis. 63 participants in the placebo group and 62 participants in the valaciclovir group who had evaluable efficacy data were analysed. There were no data on the number of originally randomised participants in each group
Interventions	• A: oral valaciclovir 2 g to be taken within 1 hour of the dental procedure, a second 2 g dose of valaciclovir to be taken the evening of the dental procedure, as well as 2 1 g doses to be taken 12 hours apart the next day • B: placebo to be taken at the same schedule as valaciclovir The trialists determined compliance via oral confirmation by the participant that all medication had been taken according to the prescribed schedule and with the return of the empty pill bottle
Outcomes	1. Percentage of participants who experienced a recurrence within 1 week after the dental procedure 2. Percentage of participants who shed HSV in saliva 3. Evaluation of lesion severity (1 = papule, 2 = vesicle, 3 = ulcer) 4. Duration of lesion healing and episode 5. Time to pain cessation

Miller 2004 *(Continued)*

	6. Adverse events
Notes	Setting: a university hospital Country: US Funding source: GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "We assigned patients sequentially to the study medication, which was numbered according to a computer-generated randomized code. Three randomization codes were used per treatment group based on lesion frequency categories. Category 1 was composed of patients with a history of one lesion per year; category 2, patients with a history of two to four lesions per year; and category 3, patients who had a history of more than four lesions per year"
Allocation concealment (selection bias)	Low risk	Quote: "We assigned patients sequentially to the study medication, which was numbered according to a computer-generated randomized code"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "For the double-blinded study medications, we packaged 12 pills per identical white bottle"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The treatment blind was maintained throughout the trial and was not broken for any subject"
Incomplete outcome data (attrition bias) All outcomes	Low risk	23 (15.5%) of 148 eligible participants were lost to follow up
Selective reporting (reporting bias)	Low risk	Both efficacy and adverse outcomes were reported
Other bias	Unclear risk	There was insufficient information to permit judgement

Mills 1987

Methods	This was a randomised trial
Participants	Volunteers were recruited for this study from physicians, medical scientists, medical personnel, and their spouses attending week-long conferences at 3 United States ski resorts **Inclusion criteria** • Had a history of recurrent orofacial herpes that was triggered by skiing **Exclusion criteria** • Participants with present or past skin cancer, albinism, allergy to sunscreens or aciclovir, immunosuppression (due to disease or medication), atopic dermatitis, photodermatitis, or those undergoing current antiviral therapy were excluded, as were individuals who in the 3 weeks prior to entry had been skiing or had had heavy sun exposure

Mills 1987 *(Continued)*

	• Participants with reactivation of herpes labialis within the past week or with active lesions also were excluded For the purposes of randomisation, participants were stratified into those with a self-perceived risk of developing herpes labialis after 3 days of skiing of greater than 75%, 50% to 75%, or less than 50%. A total of 51 participants were enrolled: 29 at conference 1, 14 at conference 2, and 8 at conference 3. 24 participants received sunscreen, and 27 received placebo
Interventions	• A (sunscreen group): a UVA or UVB sunscreen containing PABA (as padimate 0) and a benzophenone (as oxybenzone) with a SPF of 15 • B (placebo group): an identical placebo The study medication was supplied both in lipstick form and as a lotion. The participants applied the study medication (both lipstick and lotion) hourly, immediately before and during skiing each day for the 6 days of the study
Outcomes	1. Number of participants with recurrence of HSL 2. Lesion size of recurrent HSL
Notes	Setting: conferences held at ski resorts Country: US Funding source: Herbert Laboratories and Dorsey Laboratories

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...according to a blocked and stratified randomization scheme"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Neither subjects nor investigators knew the identity of the study medications"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The code was not broken until after the data had been analyzed"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study
Selective reporting (reporting bias)	High risk	Only efficacy data on the number of participants having a recurrence were reported. The trials did not provide respective data on the mean lesion size of the 2 groups
Other bias	Unclear risk	There was insufficient information to permit judgement

Møller 1997

Methods	This was a double-blind randomised trial

Møller 1997 *(Continued)*

Participants	**Inclusion criteria** • Adults with at least 5 episodes of herpes labialis per year **Exclusion criteria** • Aged under 18 years of age; those who were immunosuppressed, pregnant, or who planned pregnancy during the observation period; those with known allergy to ingredients in the vaccine; and those who had already been vaccinated against yellow fever 24 persons with culture-proven herpes labialis, with 12 in each group, were included in the study
Interventions	• A: yellow fever vaccination • B: placebo (saline)
Outcomes	1. Incidence of HSL after use of the preventative intervention (participant-reported number of attacks during the period 1 year following the intervention) 2. Adverse events
Notes	Setting: hospital Country: Denmark Funding source: not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was done by drawing lots
Allocation concealment (selection bias)	Low risk	Randomisation was done by drawing lots
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (translated): "double-blind"; "the vaccinating physician had not participated in patient selection, and he was not at the subsequent follow-up of the patients"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The blinded participant returned a mail every other month, reporting the number of attacks during the previous 2 months
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote (translated): "All 24 patients completed the study, including the 12-month follow-up"
Selective reporting (reporting bias)	Low risk	Both efficacy and adverse outcomes were reported
Other bias	Unclear risk	There was insufficient information to permit judgement

Pazin 1979

Methods	This was a double-blind randomised trial

Pazin 1979 *(Continued)*

Participants	**Inclusion criteria** • Patients admitted for microvascular decompression of the trigeminal sensory root, had a history of herpes labialis, and had no medical contraindication to participation **Exclusion criteria** • None reported 42 persons were enrolled, but 3 in the placebo group and 2 in the interferon group had to be dropped from the study or omitted from the analysis. The causes were deferral of operation (2 persons), asymptomatic excretion of HSV on the day before operation (2), and change to a different operation (1). 19 were treated with interferon and 18, with placebo
Interventions	• A (interferon group): human leukocyte interferon 70,000 U per kg of body weight per day was administered intramuscularly in the morning and evening for 5 days beginning on the day before the operation • B (placebo group): equivalent volumes of human serum albumin (the interferon vehicle) Both groups received high-dose corticosteroid therapy before and after operation. Dexamethasone 10 mg was administered at the same time as the initial interferon or placebo injection, and approximately 90 mg of dexamethasone was administered over the ensuing 90 hours
Outcomes	1. Incidence of HSL during use of the preventative intervention 2. Adverse effects during use of the preventative intervention 3. Severity (lesion area, stage, pain) of attack of recurrent HSL during use of the preventative intervention
Notes	Setting: hospital Country: US Funding source: US National Health Institute

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A paired randomisation schedule was used
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The study was double blinded" Comment: interferon and equivalent volumes of albumin were administered, respectively
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The study was double blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 (12%) of 42 enrolled participants did not complete the trial because of a cause unrelated to efficacy, with 3 (14%) in the placebo group and 2 (10%) in the interferon group
Selective reporting (reporting bias)	Low risk	Both efficacy and adverse outcomes were reported
Other bias	Unclear risk	There was insufficient information to permit judgement

Pedersen 2001

Methods	This was a double-blind, randomised, placebo-controlled trial
Participants	**Inclusion criteria** • Participants with a self-described history of recurrent herpes labialis **Exclusion criteria** • None reported A total of 52 persons with an estimated average number of recurrent herpes labialis in the preceding year of 10.3 (range 4 to 45) were enrolled, with 27 in the LongoVital® (LV) group and 25 in the placebo group. 3 persons withdrew before the end of the study for reasons unrelated to the medication
Interventions	• A (LV group): intake of 3 tablets or capsules of LV every morning for 4 months • B (placebo group): intake of 3 tablets or capsules of placebo every morning for 4 months Both groups were followed up without study medications for another 4 months
Outcomes	1. Number of recurrent herpes labialis outbreaks 2. Duration of pain/discomfort from the lesions (from when itching first appeared until '0' was registered on the visual analogue scale) 3. Maximal visible size of lesions 4. Subjective all-over evaluations of number, duration, and pain/discomfort from recurrent herpes labialis 5. Subjective evaluation of all-over period of preference In the previous studies with LV, it has taken 2 months before any benefit was demonstrated. Therefore, the various statistics were evaluated in periods of 2 months during both the treatment and post-treatment follow-up periods in this study, i.e., days 0 to 60, days 61 to 120, days 121 to 180, and days 181 to 240
Notes	Setting: Oral Medicine Clinic Country: Denmark Funding source: Paramedical A/S

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The methods of randomisation were not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "...double-blind" Quote: "The LV tablets were coated to make them indistinguishable from the inert lactose, placebo tablets"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcomes were assessed and reported by the blinded participants

Pedersen 2001 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	3 (6%) of 52 participants withdrew before the end of the study for reasons unrelated to the medication
Selective reporting (reporting bias)	High risk	Pain was measured by visual analogue scale, but the results were not reported. In the follow-up period, the duration of herpes labialis episodes and maximal size of herpetic lesions in the LongVital group were greater than the placebo group, but the authors did not report or make statistical comparisons
Other bias	High risk	The estimated number of recurrent herpes labialis episodes the year before the study tended to be higher in the placebo group (P = 0.09)

Pfitzer 2005

Methods	This was a randomised trial
Participants	**Inclusion criteria** • Presenting a medical diagnosis of herpes disease (with an average frequency of occurrence of at least 5 times per year or more than 10 days of persistent symptoms) **Exclusion criteria** • Suffering from severe immune diseases or taking immunosuppressive medication (cortisone treatment, cancer, chemotherapy, transplant patients) A total of 21 participants were classified according to the frequency of occurrence in 3 different categories (I = 5 times per year, II = 6 to 12 times/year, and III = > 12 times/year). Within these categories, they were randomised to an experimental (n = 10) and a control group (n = 11)
Interventions	• A (hypnotherapy): 5 weekly individual therapy sessions of symptom-oriented treatment and instructions to improve stress-coping skills and management of aversive emotions • B (control): no hypnotherapy
Outcomes	1. Scale for assessing the disease to document the frequency and intensity of symptoms 2. Visual analogue scales to capture the subjective impact (appearance and pain) from 0 ("no impairment") to 10 ("the most conceivable expression") 3. Stress-processing questionnaire to assess stress-coping mechanisms 4. Marburger skin questionnaire to measure skin disease-related subjective strain 5. Perceptions of control questionnaire The final assessment took place 6 months after treatment
Notes	Setting: Psychological Institute of the University of Tübingen Country: Germany Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The methods of randomisation were not reported

Pfitzer 2005 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was impossible as hypnotherapy was used
Blinding of outcome assessment (detection bias) All outcomes	High risk	The unblinded participants assessed the outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No dropouts or withdrawals were mentioned
Selective reporting (reporting bias)	Low risk	All of the outcomes specified in the Methods were reported
Other bias	Unclear risk	There was insufficient information to permit judgement

Raborn 1997

Methods	This was a double-blind, randomised, placebo-controlled, multicentre trial
Participants	**Inclusion criteria** • Normal, healthy volunteers of either gender who were over the age of 18 years and who had experienced more than 3 episodes of sun-induced herpes labialis during the previous year **Exclusion criteria** • Pregnant and nursing mothers; people who had received antiviral medication during the week leading up to the study; people with known psychiatric disorders; people with underlying medical or surgical disorders that might alter their susceptibility to herpes simplex virus infections; or people with histories of eczema herpeticum, atopic dermatitis, or other skin conditions that would predispose them to eczema herpeticum A total of 196 participants were enrolled. 5 enrolled participants who did not receive medication were excluded from the analysis. The remaining 191 participants (95 treated with aciclovir, 96 given the placebo) constituted the intent-to-treat group and were included in the safety and efficacy analysis. Of these 191 participants, 10 were excluded from the efficacy subset for various protocol violations that ranged from using lipstick while skiing to applying the study medication less than 12 hours before sun exposure. A separate efficacy analysis was conducted for the remaining 181 participants (91 aciclovir, 90 placebo)
Interventions	• A: aciclovir 5% cream • B: placebo cream The participants were given the study drug to apply 12 hours before intensive sun exposure (in other words, during the evening preceding the day they would start to ski). The study drug was applied 5 times per day: at bedtime, on waking, and 3 times during the course of the day at 4-hour intervals. This treatment continued for a period of at least 72 hours, to a maximum of 168 hours
Outcomes	1. Herpes labialis during the treatment period and during the 4-day follow-up 2. Estimates of time-to-first lesion for the treatment period and the treatment period plus 4 days' follow-up

Raborn 1997 *(Continued)*

	3. Duration of pain Each participant was contacted daily and examined within 24 hours by a dentist, physician, physician assistant, or nurse if signs or symptoms of recurrent disease appeared. Each participant was contacted either by mail or by phone 7 to 10 days after completing the study to determine whether there were any problems and to note any formation of lesions since discontinuation of the study drug
Notes	Setting: 7 ski sites Country: Canada and the US Funding source: Burroughs Wellcome, Canada

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The methods of randomisation were not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The subjects and all of the study personnel were blinded as to which treatment was being applied to which person"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The subjects and all of the study personnel were blinded as to which treatment was being applied to which person"
Incomplete outcome data (attrition bias) All outcomes	Low risk	15 (7.7%) of 196 enrolled participants did not complete the trial or violated the protocol
Selective reporting (reporting bias)	High risk	The authors assessed pain and found no significant differences in the amount of pain between the aciclovir and placebo groups. However, the authors did not report the statistics
Other bias	Unclear risk	There was insufficient information to permit judgement

Raborn 1998

Methods	This was a randomised, double-blind, placebo-controlled trial
Participants	**Inclusion criteria** • Volunteers who were at least 18 years of age and had histories of recurrent herpes labialis triggered by sun exposure and a self-perceived risk of the development of labialis after sun exposure that was 50% or greater **Exclusion criteria** • Active herpes lesions at time of enrolment; use of antiviral medication within 7 days of participation; aciclovir allergies; eczema, atopic dermatitis, or other skin conditions that might predispose them to eczema herpeticum; pregnant women; nursing mothers; and fertile and sexually active women not using adequate contraceptive measures

Raborn 1998 *(Continued)*

	239 persons were enrolled, but 2 who did not receive the test drug were excluded from analysis by the trialists. 114 received aciclovir, and 123 received placebo
Interventions	• A: oral aciclovir • B: placebo Participants (all of whom were at least 18 years of age) were given 800 mg of the study drug twice daily (1600 mg daily) beginning 12 to 24 hours before sun exposure, with the same dosage continuing for the entire sun-exposure period (minimum: 3 days; maximum: 7 days). They were required to complete at least 3 hours of outdoor activity (downhill or cross-country skiing) for at least 3 days, allowed to use acetaminophen as an analgesic, and provided with and encouraged to use a standard sunscreen (in lipstick form) with a sun prevention factor of 15
Outcomes	1. Recurrence of herpes labialis during use of the preventative intervention (researcher-diagnosed) 2. Adverse effects during use of the preventative intervention 3. Severity (lesion size, stage, and pain) of recurrent herpes labialis during use of the preventative intervention 4. Participant's subjective sensation in comparison to previous recurrences (noted as "same as usual", "worse than usual," "better than usual")
Notes	Setting: 3 centres Country: Canada Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "...double-blind, placebo-controlled" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...double-blind, placebo-controlled" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 (0.8%) of 239 enrolled persons did not receive the test drug and were excluded from analysis by the trialists
Selective reporting (reporting bias)	Low risk	Efficacy and safety outcomes were reported in detail
Other bias	Unclear risk	There was insufficient information to permit judgement

Redman 1986

Methods	This was a double-blind, placebo-controlled, randomised trial
Participants	**Inclusion criteria** • Adults who had at least 4 outbreaks of herpes labialis per year for at least 2 years **Exclusion criteria** • None reported 100 healthy adults participated in this trial; 84 participants returned their report forms, giving a response rate of 84%
Interventions	• A: immune serum globulin • B: dilute (1:5000) histamine solution The participants were given a single 0.2 ml intradermal injection of the study drug in the anterior midforearm
Outcomes	1. Number of herpes labialis outbreaks 2. Number of days to vesicle healing 3. Severity of herpes labialis outbreaks The participants were given a report form to record the above data for 6 months following the treatment and were asked to post the form back to the researcher
Notes	Setting: a family practice Country: US Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "...placebo-controlled double-blind" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The blinded participants assessed the outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	16 (16%) out of 100 participants did not return their report form
Selective reporting (reporting bias)	High risk	Only efficacy outcomes were assessed and reported. The SDs of the frequency of recurrences before and after treatment were not provided
Other bias	Unclear risk	There was insufficient information to permit judgement

Rooney 1991

Methods	This was a double-blind, placebo-controlled, cross-over trial
Participants	**Inclusion criteria** • Otherwise healthy adults aged 18 to 60 with a history of recurrent herpes labialis at least once per year and who were seropositive for HSV **Exclusion criteria** • Participants who had used antiviral agents within 30 days before enrolment and those with contact hypersensitivity to para-aminobenzoic acid (PABA)-based sunscreens A total of 38 participants were enrolled
Interventions	• A (sunscreen): a commercially available preparation ('Total Eclipse AB', Eclipse Laboratories, Lynchburg, Virginia, US) consisting of 2% to 8% glyceryl p-aminobenzoate (UVB absorber), 3.3% padimate 0 (UVB absorber), and 5% to 6% oxybenzone (UVA absorber) in an alcohol base, with a sun protection factor of 15 • B (placebo): a matched solution without active sunscreens Each participant received 1 exposure with sunscreen and 1 with placebo, the order of administration being randomised (by Efron's biased coin method) and double blind. A solution of sunscreen or placebo was applied to the exposure site and was allowed to dry before exposure to UV light. The minimum time between UV exposures or between previous HSV recurrence and UV exposure was 3 weeks
Outcomes	1. UV-induced recurrence (researcher-diagnosed), defined as a clinically or virologically confirmed (or both) HSV outbreak developing within 7 days of UV exposure and located within 1 cm of the exposure site
Notes	Setting: 2 medical centres (the Clinical Centre of the National Institutes of Health and the University of California Los Angeles Hospital) Country: US Funding source: not mentioned, but Eclipse Laboratories provided the placebo

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised by Efron's biased coin method
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "double blind" Quote: "The study code was broken only after all UV exposures were completed" Quote: "As a control for the blinding investigators and patients were asked to guess which treatment was given 3 days after UV exposure" Quote: "In the assessment of the blinding, both investigators and patients could correctly identify placebo in over 80% of cases"

Rooney 1991 *(Continued)*

		Comment: although the trialists made efforts in blinding, placebo recipients had sunburn while none of the sunscreen recipients had sunburn. Participants and researchers might thus have known the assigned treatments
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "double blind" Quote: "The study code was broken only after all UV exposures were completed" Quote: "In the assessment of the blinding, both investigators and patients could correctly identify placebo in over 80% of cases" Comments: participants and researchers might have known the assigned treatments because of the presence of sunburn
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants (5%) out of 38 enrolled participants withdrew from the study after 1 exposure with placebo - 1 because of pregnancy and 1 because of relocation for a new job. Another 1 was excluded from the analysis because of violation of the protocol. Thus, a total of 38 placebo and 35 sunscreen exposures were analysed
Selective reporting (reporting bias)	High risk	Only efficacy outcomes were assessed and reported
Other bias	Unclear risk	There was insufficient information to permit judgement

Rooney 1993

Methods	This was a randomised, placebo-controlled, cross-over trial
Participants	**Inclusion criteria** • Otherwise healthy adults aged 18 to 50 who reported histories of 6 or more episodes of herpes labialis per year **Exclusion criteria** • None reported 56 people entered a pretreatment 4-month observation phase. 22 participants who had 2 or more recurrences of herpes labialis were randomised
Interventions	• A: aciclovir 400 mg twice daily for 4 months, then switched to placebo twice daily for 4 months • B: placebo twice daily for 4 months, then switched to aciclovir 400 mg twice daily for 4 months
Outcomes	1. Recurrence of herpes labialis (researcher-diagnosed) 2. Time to first recurrence 3. Duration of attack of recurrent herpes labialis (posthoc analysis, not a prespecified outcome) 4. Rate of adherence to the preventive intervention
Notes	Setting: a medical centre (the Clinical Centre of the National Institutes of Health) Country: US Funding source: Partly from Burroughs Wellcome Company
Risk of bias	

Rooney 1993 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind" Comments: matched placebo provided by the pharmaceutical company was administered in the same regimen
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 (9.1%) out of 22 participants who received aciclovir in the first phase did not complete the study and were excluded from analysis
Selective reporting (reporting bias)	High risk	Only efficacy outcomes were reported
Other bias	High risk	There was no washout period between the 2 phases of the study. The trialists excluded recurrences that occurred during the first week of each treatment phase, but the duration might have been too short

Russell 1978

Methods	This was a double-blind placebo-controlled trial
Participants	**Inclusion criteria** • Had recurrent circumoral herpes at least 4 times a year **Exclusion criteria** • None reported A total of 99 participants were randomised, with 48 in the levamisole group and 51 in the placebo group. 27 participants did not complete the trial (19 in the levamisole group and 8 in the placebo group)
Interventions	• A (levamisole): 2.5 mg/kg of body weight rounded off to the nearest 50 mg and was usually 150 mg/kg • B (placebo) The treatment drugs were taken on 2 consecutive days each week for 6 months
Outcomes	1. Frequency of herpes labialis episodes 2. Number of days required for disappearance of scabs 3. Subjective estimate of size and severity of the lesion when compared with lesions that had occurred before treatment 4. A complete haematological assessment; urinalysis; and assay of serum proteins, calcium, phosphate, alkaline phosphatase, transaminases, urea, and creatinine every 2 months

Russell 1978 *(Continued)*

	5. Immune response to herpes simplex virus was assessed every 2 months by lymphocyte transformation and antibody-dependent, cell-mediated immunity with use of a constant control serum (methods that assess the immune response to the herpes simplex virus)
Notes	Setting: a university hospital Country: Canada Funding source: supported in part by a grant from the Medical Research Council of Canada

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "a double-blind, controlled trial" Quote: "The placebo and active drug were structurally identical and taken on two consecutive days each week"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcomes were assessed and reported by the participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Of the 99 participants, 27 (27.2%) did not complete the trial and were excluded from the analysis, with 19 (39.6%) in the levamisole group and 8 (15.7%) in the placebo group
Selective reporting (reporting bias)	Low risk	Both efficacy and adverse outcomes were reported
Other bias	High risk	The baseline frequency of HSL in the levamisole group was higher than that in the placebo group (4.8 ± 2.7 versus 3.4 ± 1.8 during a 6-month period before treatment)

Schindl 1999

Methods	This was a randomised placebo-controlled trial
Participants	**Inclusion criteria** • Had recurrent perioral herpes simplex infection, defined as at least 1 herpes attack per month for more than 6 months independent of any known triggering mechanism such as fever, sun exposure, or menstruation. All participants had had at least 1 course of treatment with oral aciclovir (800 mg per day) for 4 weeks, which had been completed at least 3 months before enrolment **Exclusion criteria** • Current antiviral or immunosuppressive therapy, homeopathy, or acupuncture as well as human immunodeficiency virus infection

Schindl 1999 *(Continued)*

	A total of 50 participants were enrolled, but 2 did not complete the study (1 each in the laser and placebo group). 48 participants completed the study, with 24 in each group
Interventions	All participants in both groups were treated by the same physician • A (laser group): participants received low-intensity laser therapy by means of an 80 mW, 690 nm continuous wave diode laser (Helbo Lasers, Gallspach, Austria). Irradiations (exposure time: 10 minutes; area: 1 cm^2; intensity: 80 mW/cm^2; dose: 48 J/cm^2) once daily for 2 weeks at the site of original chronic herpes infection. In those participants with herpes infections located on both the upper and lower lip, both sites were irradiated • B (placebo group): the placebo irradiation was performed in the same manner as in the laser group except that the laser was not turned on
Outcomes	1. The median recurrence-free intervals observed during a 52-week follow-up period 2. Side-effects
Notes	Setting: a university hospital Country: Austria Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	All participants in both groups were treated by the same physician. Participants in both groups wore non-transparent protection glasses during the procedure
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The evaluator was not aware of the study protocol"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Two of 50 enrolled subjects did not complete the study: one patient of the placebo group discontinued because of time problems and one patient of the laser group had to undergo an appendectomy"
Selective reporting (reporting bias)	Unclear risk	Efficacy and adverse outcomes were reported
Other bias	High risk	No scheduled follow-ups were planned, but the participants were told to return to the clinic at the time of recurrence

Schädelin 1988

Methods	This was a randomised placebo-controlled trial
Participants	**Inclusion criteria**

Schädelin 1988 *(Continued)*

	• Participants admitted to a neurosurgical unit for trigeminal surgery (glycerol injection) **Exclusion criteria** • Participants with active herpes, antiviral therapy within 2 months prior to surgery, or presence of significant renal impairment A total of 30 participants entered and completed the study, including 14 assigned to the aciclovir group and 16 to the placebo group
Interventions	• A (aciclovir group): 2 daily oral doses of 400 mg starting on the evening prior to surgery and continued for 5 days • B (placebo group): placebo administered by the same regimen as the aciclovir group
Outcomes	1. Presence of herpes simplex infection by clinical examination. The participants were examined daily usually until the third postoperative day during their stay in hospital. They were then required to complete a diary noting signs and symptoms of herpes labialis until the first follow-up visit approximately 4 weeks later 2. Presence of herpes simplex infection by culture at the 3rd postoperative day 3. Side-effects
Notes	Setting: a university hospital Country: Switzerland Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A randomisation list was used for assigning the participants
Allocation concealment (selection bias)	Low risk	The randomisation list was not revealed to the investigators until submission of the results
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The investigators and participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigators were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled 30 participants completed the study
Selective reporting (reporting bias)	Low risk	Efficacy and adverse outcomes were reported
Other bias	High risk	Only 13 (43%) of the 30 participants had a history of herpes labialis

Senti 2013

Methods	This was a randomised placebo-controlled trial
Participants	**Inclusion criteria** • Aged 18 to 50 years and had experienced at least 8 herpes labialis relapses in the previous year **Exclusion criteria** • Women of child-bearing potential who were not using a reliable method of birth control; pregnant or breastfeeding women; people with a medical history of immunosuppression by radiotherapy, chemotherapy, immunomodulatory drugs, or HIV; people participating in another clinical study; people with a medical history of any severe disease like hepatitis, cardiovascular or gastrointestinal disease, renal or liver dysfunction, malignancies, or psychiatric disorder; people using antiviral drugs, systemic anti-inflammatory medications, or steroids; people suffering from eczema herpeticum or any abnormal perioral skin condition A total of 40 participants were randomised, including 20 assigned to the 2-hydroxypropyl-β-cyclo dextrin (2-HPβCD) group and 20 to the placebo group. Of them, 2 (10%) in the 2-HPβCD group and 4 (20%) in the placebo group did not complete the study
Interventions	• A (2-HPβCD group): topical application of the 2-HPβCD gel (2-HPβCD 20% dissolved in a mixture of various types of polyethylene glycols (PEGs)) to the lips twice daily for 6 months • B (placebo group): topical application of the placebo gel (a mixture of the same PEGs used for the 2-HPβCD gel) to the lips twice daily for 6 months
Outcomes	1. Primary outcome: number of herpes labialis relapses 1. Secondary outcomes: a. Safety and tolerability of the HPβCD 20% gel as well as the maximal lesion area b. The duration of the herpes relapse episodes c. The degree of pain during a relapse episode
Notes	Setting: Clinical Trials Center Zurich Country: Switzerland Funding source: Devirex AG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The investigators and participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The study remained blinded until after the database was unlocked
Incomplete outcome data (attrition bias) All outcomes	Low risk	• 16 (80%) and 18 (90%) participants in the 2-HPβCD and placebo group, respectively, completed the study

Senti 2013 *(Continued)*

		• In the 2-HPβCD group, 2 participants withdrew consent. In the placebo group, 1 participant was lost to follow up, 1 participant was excluded after 2 days of study participation due to an adverse event (strong perioral pruritus already after first application), 1 participant was excluded because of lack of compliance, and 2 participants withdrew consent
Selective reporting (reporting bias)	Unclear risk	The study protocol is available on ClinicalTrials.gov (identifier: NCT00914745). The prespecified primary outcome (the number of herpes labialis relapse) was reported. However, the exact numerical data were not provided; the authors only provided the data in plots
Other bias	Unclear risk	There was insufficient information to permit judgement

Spruance 1988

Methods	This was a randomised placebo-controlled trial
Participants	**Inclusion criteria** • Registrants for medical conferences to be held at ski resorts at Snowbird, Utah (centre 1) and at Steamboat Springs, Colorado (centre 2) who had a history of sun-induced herpes labialis **Exclusion criteria** • Not using adequate contraception if female • Had serious underlying medical illness • Were pregnant, nursing, or taking other antiviral medications • Had a history of allergy to aciclovir Study participants were stratified prospectively according to their self-perceived risk of herpes labialis while skiing (> 50% or < 50% chance). 153 participants were enrolled, but 6 did not return for clinical evaluation. A total of 101 high-risk participants (52 in the aciclovir group and 49 in the placebo group) and 46 low-risk participants (23 in each group, respectively) completed the study and were analysed
Interventions	• A (aciclovir) • B (placebo) Participants were instructed to take 2 200 mg capsules of the study medication twice a day, beginning 12 hours prior to their first anticipated sun exposure. Therapy was continued throughout the period of skiing, up to a maximum of 7 days. A standard sunscreen of sun protection factor 15 was provided to all participants, and frequent use was advised
Outcomes	1. Participants were seen daily during the treatment period to determine the presence or absence of lesions. Developing lesions were characterised according to lesion stage, size, and pain (on a scale of 0 to 4+), and a swab specimen of the lesion was obtained for virus isolation. 2 to 4 weeks after completion of the study, participants were contacted by mail to determine the development of any lesions in the post-treatment period
Notes	Setting: 2 ski resorts Country: US Funding source: Burroughs Wellcome & Co.

Risk of bias

Bias	Authors' judgement	Support for judgement

Spruance 1988 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	The method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Burroughs Wellcome & Co. provided 200 mg capsules of aciclovir (Zovirax®) and identical placebo capsules that were randomised among serially numbered bottles
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigators were unaware of the assigned treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	6 out of 153 (3.9%) enrolled participants did not return for evaluation and were excluded from the analysis
Selective reporting (reporting bias)	Low risk	Efficacy and adverse outcomes were reported
Other bias	Low risk	A standard sunscreen of sun protection factor 15 was provided to all participants, and frequent use was advised. The trialists found no relation between the development of herpes and the potential confounding factors including skin type, pre-existing tan, pre-existing burn, facial hair, history of recent heavy sun exposure, history of skiing on the date of enrolment, frequency of herpes labialis, susceptibility to sun-induced recurrences, hours of sun exposure during the treatment period, number of sunscreen applications during the treatment period, and degree of sunburn

Spruance 1991a

Methods	An article reported 3 randomised trials included in this review, including 2 on oral aciclovir and 1 on topical aciclovir for prophylaxis of ultraviolet radiation (UVR)-induced herpes labialis. We labelled the 3 included trials as Spruance 1991a, Spruance 1991b, and Spruance 1991c, respectively. The article also reported 1 trial on early oral aciclovir treatment begun 48 hours after UVR exposure, but we excluded the trial from this review as aciclovir was used as treatment
Participants	**Inclusion criteria** • Individuals with a typical clinical history of recurrent herpes labialis: episodes of vesicular lesions on the vermilion border of the lips or on the perioral skin. In addition, the etiology of the lesions was documented in every instance by prior isolation of HSV from lesion samples. All participants had a history of reactivation of herpes labialis by exposure to sunlight and had a history of lesion usually occurring on 1 specific area of the lips. All participants were ≥ 18 years old and in good general health. All women had a negative urine pregnancy test and used adequate means of contraception during the trial period **Exclusion criteria** • Had used an antiviral medication in the preceding 4 weeks A total of 30 participants were enrolled in this trial, with an equal number of participants randomised to the active treatment and placebo groups, respectively
Interventions	Peroral study 1:

Spruance 1991a *(Continued)*

- A (aciclovir): treated for 7 days with aciclovir capsules (200 mg, 5 times/day), beginning immediately after UVR exposure
- B (placebo): treated for 7 days with placebo capsules, beginning immediately after UVR exposure

Outcomes	The outcome data of the 2 peroral studies, Spruance 1991a and Spruance 1991b, were combined because of similar results 1. Incidence of herpes labialis during use of the preventative intervention: participants were studied every other day for 4 visits for evidence of herpes labialis. The exact time of lesion onset was obtained historically by participant interview and was defined as the participant's first awareness of a papule or induration 2. Severity (lesion area, stage, pain) of attack of recurrent herpes labialis during use of the preventative intervention: clinical assessment of lesion severity was made by observation of lesion stage, size, and pain
Notes	Setting: university hospital (the University of Utah School of Medicine) Country: US Funding source: Burroughs Wellcome & Co. and National Institutes of Health

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Gelatin capsules (Eli Lilly, Indianapolis) were filled with 200 mg of ACV from commercially available capsules (Burroughs Wellcome) or lactose placebo compound and randomly allocated to serially numbered bottles. The drug code for topical and peroral clinical trial materials was concealed from both patients and investigators until the end of the study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As mentioned above, the evaluating investigators were blinded to the treatments
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No dropouts or withdrawals were mentioned
Selective reporting (reporting bias)	High risk	Only efficacy outcomes were reported. The severity data were not reported
Other bias	Unclear risk	There was insufficient information to permit judgement

Spruance 1991b

Methods	This was a randomised trial on oral aciclovir for prophylaxis of ultraviolet radiation (UVR)-induced herpes labialis, which was reported along with Spruance 1991a and Spruance 1991c in the same article
Participants	**Inclusion criteria**

Spruance 1991b *(Continued)*

	• Individuals with a typical clinical history of recurrent herpes labialis: episodes of vesicular lesions on the vermilion border of the lips or on the perioral skin. In addition, the etiology of the lesions was documented in every instance by prior isolation of HSV from lesion samples. All participants had a history of reactivation of herpes labialis by exposure to sunlight and had a history of lesion usually occurring on 1 specific area of the lips. All participants were ≥ 18 years old and in good general health. All women had a negative urine pregnancy test and used adequate means of contraception during the trial period **Exclusion criteria** • Had used an antiviral medication in the preceding 4 weeks A total of 36 participants were enrolled, with an equal number of participants randomised to the active treatment and placebo groups, respectively
Interventions	Peroral study 2: • A (aciclovir): treated for 14 days with aciclovir capsules (200 mg, 5 times/day), beginning 7 days before UVR exposure • B (placebo): treated for 14 days with placebo capsules, beginning 7 days before UVR exposure
Outcomes	The outcome data of the 2 peroral studies, Spruance 1991a and Spruance 1991b, were combined because of similar results 1. Incidence of herpes labialis during use of the preventative intervention: participants were studied every other day for 4 visits for evidence of herpes labialis. The exact time of lesion onset was obtained historically by participant interview and was defined as the participant's first awareness of a papule or induration 2. Severity (lesion area, stage, pain) of attack of recurrent herpes labialis during use of the preventative intervention: clinical assessment of lesion severity was made by observation of lesion stage, size, and pain
Notes	Setting: university hospital (the University of Utah School of Medicine) Country: US Funding source: Burroughs Wellcome & Co. and National Institutes of Health

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Acyclovir 5% cream and placebo cream were provided in identically appearing 15-g tubes by Burroughs Wellcome (Research Triangle Park, NC)... The drug code for topical and peroral clinical trial materials was concealed from both patients and investigators until the end of the study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As mentioned above, the evaluating investigators were blinded to the treatments
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No dropouts or withdrawals were mentioned

Spruance 1991b *(Continued)*

Selective reporting (reporting bias)	High risk	Only efficacy outcomes were reported. The severity data were not reported
Other bias	Unclear risk	There was insufficient information to permit judgement

Spruance 1991c

Methods	This was a randomised trial on topical aciclovir for prophylaxis of ultraviolet radiation (UVR)-induced herpes labialis, which was reported along with Spruance 1991a and Spruance 1991b in the same article
Participants	**Inclusion criteria** • Individuals with a typical clinical history of recurrent herpes labialis: episodes of vesicular lesions on the vermilion border of the lips or on the perioral skin. In addition, the etiology of the lesions was documented in every instance by prior isolation of HSV from lesion samples. All participants had a history of reactivation of herpes labialis by exposure to sunlight and had a history of lesion usually occurring on 1 specific area of the lips. All participant were ≥ 18 years old and in good general health. All women had a negative urine pregnancy test and used adequate means of contraception during the trial period **Exclusion criteria** • Had used an antiviral medication in the preceding 4 weeks A total of 90 participants were enrolled, with an equal number of participants randomised to the active treatment and placebo groups, respectively
Interventions	Topical study: • A (aciclovir): apply aciclovir 5% cream to the UVR zone every 2 hours while awake, for 7 days beginning immediately after UVR exposure • B (placebo): apply vehicle control cream to the UVR zone every 2 hours while awake, for 7 days beginning immediately after UVR exposure
Outcomes	The outcome data of the 2 peroral studies were combined because of similar results 1. Incidence of herpes labialis during use of the preventative intervention: participants were studied every other day for 4 visits for evidence of herpes labialis. The exact time of lesion onset was obtained historically by participant interview and was defined as the participant's first awareness of a papule or induration 2. Severity (lesion area, stage, pain) of attack of recurrent herpes labialis during use of the preventative intervention: clinical assessment of lesion severity was made by observation of lesion stage, size, and pain
Notes	Setting: university hospitals (the University of Utah School of Medicine, the University of Michigan School of Dentistry, and the Graduate School of Public Health, University of Pittsburg) Country: US Funding source: Burroughs Wellcome & Co. and National Institutes of Health

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of randomisation was not reported

Spruance 1991c *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Acyclovir 5% cream and placebo cream were provided in identically appearing 15-g tubes by Burroughs Wellcome (Research Triangle Park, NC)... The drug code for topical and peroral clinical trial materials was concealed from both patients and investigators until the end of the study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As mentioned above, the evaluating investigators were blinded to the treatments
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No dropouts or withdrawals were mentioned
Selective reporting (reporting bias)	High risk	Only efficacy outcomes were reported
Other bias	Unclear risk	There was insufficient information to permit judgement

Spruance 1999

Methods	This was a double-blind, dose-ranging, placebo-controlled, multicentre trial
Participants	**Inclusion criteria** • ≥ 18 years old and had a self-described history of recurrent herpes labialis (vesicular lesions on the vermilion border of the lips or perioral skin) following sun exposure • Women of childbearing age must have been using an accepted method of birth control **Exclusion criteria** • Were pregnant or breast-feeding; had a history or laboratory evidence of a significant medical disorder; had received any antiviral drug, investigational drug, or vaccine; had an episode of herpes labialis within 30 days before enrolment; or had a psychiatric disorder or were considered unreliable or unable to follow protocol directions in the opinion of the investigator A total of 243 participants who were randomised (60 in the famciclovir 125 mg group, 62 in the famciclovir 250 mg group, 61 in the famciclovir 500 mg group, and 60 in the placebo group) and took study medication comprised the intention-to-treat population
Interventions	• A: famciclovir 125 mg • B: famciclovir 250 mg • C: famciclovir 500 mg • D: placebo The participants received the study medication 3 times daily for 5 days beginning 48 hours after ultraviolet radiation exposure
Outcomes	The primary efficacy variables were: 1. the proportion of participants who developed delayed herpetic lesions (defined as herpetic lesions developed 3 to 7 days after exposure) 2. the time to healing of primary delayed classical lesions (defined as vesicles, ulcers, or hard crusts) The secondary variables included:

Spruance 1999 *(Continued)*

	1. the proportion of participants with pain 2. time to loss of pain 3. the proportion of participants with a positive virus culture 4. the maximum lesion area 5. the duration of the individual lesion stages Adherence to the medication and adverse reactions were also assessed
Notes	Setting: 5 academic medical centres Country: US and Canada Funding source: SmithKline Beecham Pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of randomisation was not reported
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomized in a double-blind fashion to receive 1 of 3 doses of famciclovir or placebo"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Study medication was provided as white film-coated tablets containing 125, 250, or 500 mg of famciclovir or matching placebo. All tablets were identical in shape, weight, and color"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above, the evaluating investigators were blinded to the treatments
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Compliance with study medication was excellent" Quote: "One placebo-treated patient was withdrawn from the study due to adverse experiences (diarrhea, nausea) that occurred on therapy and were considered related to study medication" Comments: adherence to study medication was 100% in the 3 famciclovir groups and 95% in the placebo group
Selective reporting (reporting bias)	Low risk	Both efficacy and adverse outcomes were reported
Other bias	Unclear risk	There was insufficient information to permit judgement

Thein 1984

Methods	This was a randomised, placebo-controlled, cross-over trial
Participants	**Inclusion criteria** • Healthy except for a history of at least 3 circumoral herpes lesions in the past year **Exclusion criteria** • None reported

Thein 1984 *(Continued)*

	A total of 26 participants were enrolled, with 15 in group A and 11 in group B (see below)
Interventions	• A: oral L-lysine monolysine monohydrochloride 1000 mg per day in the first 6-month period, then an identical-appearing cellulose placebo in the second 6-month period • B: placebo in the first 6-month period, then L-lysine monolysine monohydrochloride 1000 mg per day in the second 6-month period
Outcomes	1. Number of episodes of herpes labialis in the 2 6-month periods (at the initial and 6-month appointments, participants were given journals in which to record pertinent information regarding herpetic episodes) 2. Serum concentration levels of lysing and arginine at month 0, month 6, and month 12
Notes	Setting: a university hospital Country: US Funding source: Baylor College of Dentistry research grant

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The blinded participants were the outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No dropouts or withdrawals were mentioned
Selective reporting (reporting bias)	High risk	Only efficacy outcomes were reported
Other bias	High risk	There was no washout period between the 2 6-month periods

2-HPβCD: 2-hydroxypropyl-β-cyclo dextrin.
ACV: aciclovir.
GaAlAs: gallium-aluminium-arsenide.
HIV: human immunodeficiency virus.
HSL: herpes simplex labialis.
HSV: herpes simplex virus.
IFN: interferon.
LV: LongoVital®.
PABA: para-aminobenzoic acid.
PD: pentanediol.
PEGs: polyethylene glycols.
SDs: standard deviations.

SPF: sun protection factor.
UV: ultraviolet.
UVA: ultraviolet A.
UVB: ultraviolet B.
UVR: ultraviolet radiation.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alster 1999	Only 19 out of the 99 participants had a history of HSL
Altorfer 1996	This was a commentary, not a randomised trial
Armstrong	This was a review of 2 trials on the efficacy of interferon in preventing herpes simplex in renal transplant participants, not a randomised trial
Bernstein 2005	Imiquimod cream was used as a treatment rather than a preventative intervention
Blough 1983	This was a commentary, not a randomised trial
DeMaubeuge 1985	This was an uncontrolled open trial, not a randomised trial
DiGiovanna 1984	This was a trial on the therapeutic and preventive efficacy of lysine on recurrent herpes simplex infection. Only 4 out of the 20 participants had a history of herpes labialis
Donatini 2010	The participants had the option to switch therapy each month according to their satisfaction during the 6-month experiment
Dundarov 1994	This was not a randomised trial
El-Farrash 2003	This was not a randomised trial
Fawcett 1983	4 (25%) out of the 16 participants had had herpes simplex infection in the genital area or buttocks
Hellgren 1983	This was an open trial on the preventive efficacy of tromantadine in genital herpes, not a randomised trial
Jose 1980	21 (64%) of the 33 participants did not have HSL, but had genital herpes
Kalimo 1983	14 (24%) of the 58 participants did not have HSL, but had genital herpes or herpes involving other locations. The data on HSL could not be separated out from the 24% with genital herpes
Lacour 2000	This was a commentary on an included trial (Schindl 1999)
Lamey 2000	This was a trial on the therapeutic efficacy but not on the preventative efficacy of aciclovir cream
Lamura 1997	This was not a randomised trial
Likar 1968	A trial on the therapeutic efficacy but not on the preventative efficacy of 5-carboxymethyl-3-p-tolyl-thiazolidine-2,4-dione-2-acetophenonehydrazone
Milman 1980	This was a quasi-randomised cross-over trial, not a randomised trial. The participants were alternatively assigned to lysine or placebo for 12 weeks, then switched to the other treatment for another 12 weeks without a washout period
Mindel 1985	This was not a randomised trial

Study	Reason for exclusion
Munoz 2012	This was a RCT on the therapeutic efficacy of low-level laser therapy. Recurrence was assessed as a follow-up study
Myers 1975	This was a RCT on the therapeutic efficacy of photodynamic therapy on herpes simplex infection including genital herpes and herpes on other non-labial sites of the skin. Recurrence was assessed as a follow-up study
NCT00913692	The trial was terminated because of slow recruitment
Pedrazini 2007	This was a case-series study, not a randomised trial
Qadripur 1976	This was a small controlled study with 36 out of 41 participants having a history of herpes labialis. No subgroup data on those with herpes labialis were provided, and whether randomisation was applied was unknown
Queiroz Carvalho 1976	This was a case-series study, not a randomised trial
Rosenthal 1992	This was a commentary on an included trial (Rooney 1991)
Rowe 1978	This was a trial on the therapeutic efficacy but not on the preventative efficacy of topically applied vidarabine 3%
Rowe 1980	This was a trial on the therapeutic efficacy but not on the preventative efficacy of topically applied vidarabine 3% and 10%
Schmitt 1987	This was a trial on the therapeutic efficacy but not on the preventative efficacy of topical alpha interferon
Siegel 1990	This was a trial on the therapeutic efficacy but not on the preventative efficacy of a lip balm
Simon 1985	This was a randomised trial on the efficacy of lysine in preventing recurrent herpes simplex labialis or genitalis in 31 participants. However, the authors did not report how many of the 31 participants had herpes labialis
Spruance 1979	This was a trial on the therapeutic efficacy but not on the preventative efficacy of topical adenine arabinoside 5'-monophosphate
Strand 2003	This was a subgroup analysis on the occurrence of herpes labialis using the participants attending a randomised trial on valaciclovir in prevention of genital herpes transmission
Thomas 1985	In this trial, not all of the 11 participants had herpes labialis: 2 had herpes labialis, 7 had herpes labialis and herpes involving 1 or more other sites (ear, cheek, nose, finger, or thigh), and 2 had herpes simplex on the finger
Viza 1985	This was a case series including participants with labial and genital herpes
Weitgasser 1977	This was not a randomised trial
Worrall 1996	This was a commentary, not a randomised trial

HSL: herpes simplex labialis.
RCT: randomised controlled trial.

Characteristics of ongoing studies *[ordered by study ID]*

ISRCTN03397663

Trial name or title	Evaluation of the efficacy and safety of a sheabutter extract on cold sores (herpes simplex labialis)
Methods	Randomised controlled trial
Participants	**Inclusion criteria** • Participants aged between 18 and 75 years in good general health who have a clinical history of recurrent herpes labialis, with at least 6 self-reported episodes of herpes lesion in the past year and at least 1 recurrence every 3 months **Exclusion criteria** • History of immunodeficiency • Use of other antiviral agents (including herbal medications), anti-inflammatory medications, steroids, or analgesics during the treatment period • Known allergy to sheabutter • Liver function tests greater than 3 times the upper limit of normal at baseline • Female participants who are lactating, pregnant, or planning to become pregnant • Participants who have participated in another clinical trial in the last 30 days • Participants unwilling to comply with the study protocol • Any other condition that in the opinion of the investigators could compromise the study
Interventions	• Acute study: 100% sheabutter extract BSP 110 ointment versus placebo of yellow petrolatum • Maintenance study: 25% sheabutter lip balm versus 25% yellow petrolatum lip balm
Outcomes	1. Acute study: Duration of initial herpes labialis episode 1. Maintenance study: Number of herpes labialis episodes during the 6 months of the maintenance study period
Starting date	1 February 2005
Contact information	Dr Phillip Cheras, Mater Health Services, 2nd Floor, Community Health Services Building, 39 Annerley Rd, South Brisbane, 4101, Australia E-mail: philcheras@yahoo.com.au
Notes	www.controlled-trials.com/ISRCTN03397663

NCT01225341

Trial name or title	A double-blind, randomised, placebo controlled, cross-over study to assess the safety and efficacy of botulinum toxin A injections as a preventative measure for herpes labialis
Methods	Randomised controlled trial
Participants	**Inclusion criteria** • Men or women between the ages of 18 and 64 • Have herpes simplex virus 1 (HSV-1) with between 2 to 6 herpes labialis recurrences per year • Willingness and ability to comply with protocol requirements, including returning for follow-up visits and abstaining from exclusionary procedures for the duration of the study • Participants of childbearing potential must have a negative urine pregnancy test result at visit 1 and be willing and able to use an acceptable method of birth control (e.g., barrier methods used with a spermicidal agent, hormonal methods, IUD, surgical sterilisation, abstinence) during the

NCT01225341 *(Continued)*

study. Women will not be considered of childbearing potential if 1 of the following is documented on the medical history:
  * postmenopausal for at least 12 months prior to study drug administration
  * without a uterus or both ovaries or both
  * has had a bilateral tubal ligation for at least 6 months prior to study drug administration
  * absence of another physical condition according to the PI's discretion
- Willingness and ability to provide written photo consent and adherence to photography procedures (i.e., removal of jewellery and makeup)
- Willingness and ability to provide written informed consent prior to performance of any study-related procedure

Exclusion criteria

- Participants who are pregnant, nursing, planning to become pregnant, not using a reliable form of birth control, or any combination of these
- Participants with a known allergy or sensitivity to any component of the study medications or anaesthesia
- Active recurrence of herpes labialis
- Botulinum toxin in the lower 1/3 of the face within the past 6 months
- Significant concurrent illness such as diabetes, epilepsy, lupus, or congestive heart failure
- Concurrent skin condition affecting area to be treated
- Prior surgery on the area to be treated within 3 months of initial treatment or during the study
- History or evidence of keloids or hypertrophic scarring
- Current use of antivirals for the treatment of herpes labialis within 2 weeks prior to initiation of treatment (e.g., aciclovir, valaciclovir, famciclovir, and penciclovir)
- Topical use of over-the-counter medications for the treatment or prevention of HSV-1 (e.g., Abreva®)
- Participants currently using aminoglycoside antibiotics, curare-like agents, or other agents that might interfere with neuromuscular function
- Participants with a diagnosis of myasthenia gravis, Lambert-Eaton syndrome, amyotrophic lateral sclerosis, or any other disease that might interfere with neuromuscular function or current facial palsy
- Current history of chronic drug or alcohol abuse
- Concurrent therapy that, in the investigator's opinion, would interfere with the evaluation of the safety or efficacy of the study medication
- Participants who, in the investigator's opinion, have a history of poor co-operation, non-compliance with medical treatment, or unreliability
- Enrollment in any active study involving the use of investigational devices or drugs

Interventions	• Experimental (onabotulinumtoxin A/placebo): participants will be injected every 3 months with onabotulinumtoxin A for a period of 12 months. At the 12-month visit, participants will receive injections of saline • Placebo comparator (bacteriostatic normal saline/onabotulinumtoxin A): participants will be injected every 3 months with saline for a period of 12 months. At the 12-month visit, participants will receive injections of onabotulinumtoxin A
Outcomes	1. Primary outcome measures: measurement of recurrence and duration of herpes labialis lesions 1. Secondary outcome measures: measurement of lesion size, pain assessment, and symptom evaluation
Starting date	August 2010
Contact information	Steven H Dayan, MD, Medical Director, DeNova Research, Water Tower Place, 845 N Michigan Avenue, Suite 923 E, Chicago, IL 60611, US E-mail: selika@drdayan.com

NCT01225341 *(Continued)*

Notes	www.clinicaltrials.gov/show/NCT01225341

NCT01902303

Trial name or title	Evaluation of cold sore treatments on UV-induced cold sores
Methods	Randomised controlled trial
Participants	**Inclusion criteria** • Those with a clinical history of recurrent cold sores averaging 2 or more episodes per year • Those for which UV exposure is known to cause a cold sore outbreak **Exclusion criteria** • History of abnormal reactions to sunlight • Had used antiviral therapy directly prior to entering study • Any other condition that in the opinion of the Investigator may affect the results or place the participant at undue risk
Interventions	• A (BTL-TML-HSV): sublingual micro dosing of BTL-TML-HSV for 7 days • B (placebo): sublingual micro dosing of placebo for 7 days
Outcomes	1. Block the symptomatic sequence of a lesion of oral herpes simplex outbreak (visual examination of cold sores by trained evaluator and participant self assessment after exposure to UV)
Starting date	July 2013
Contact information	Elsie Kohoot, Hill Top Research, Incorporated, US E-mail: ekohoot@hill-top.com
Notes	www.clinicaltrials.gov/ct2/show/NCT01902303

NCT01971385

Trial name or title	Safety and efficacy of squaric acid dibutylester for the treatment of herpes labialis (Squarex)
Methods	Randomised controlled trial
Participants	**Inclusion criteria** • Aged > 18 • With clinical diagnosis of herpes labialis • Who self-report having 6 or more episodes of herpes labialis in the previous 12 months **Exclusion criteria** • Pregnant or lactating women • Current or recurrent infection or any underlying condition that may predispose to infection or anyone who has been admitted to the hospital due to bacteraemia, pneumonia, or any other serious infection • Therapy with glucocorticoid or immunosuppressant at time of recruitment or within past 4 weeks, except for inhaled corticosteroids for asthma

NCT01971385 *(Continued)*

	• History of malignancy (except people with surgically cured basal cell or squamous cell skin cancers who will be eligible) • History of organ transplantation • Negative HIV-positive status determined by history at screening or known history of any other immunosuppressing disease • Severe comorbidities (diabetes mellitus requiring insulin; CHF (EF < 50% at baseline will be exclusionary) of any severity; MI, CVA, or TIA within 3 months of screening visit; unstable angina pectoris; oxygen-dependent severe pulmonary disease) • Person is currently enrolled in another investigational device or drug trial(s) or has received other investigational agent(s) within 28 days of baseline visit • Persons who have known hypersensitivity to squaric acid or any of its components • History of recent alcohol or substance abuse (< 1 year) • Any condition judged by the investigator to cause this clinical trial to be detrimental to the person • History of psychiatric disease that would interfere with the person's ability to comply with the study protocol • History of non-compliance with other therapies
Interventions	• Participants with a history of recurrent herpes labialis will be sensitised with either 2% SADBE or placebo. Following this, participants sensitised with 2% SADBE will receive 2% squaric acid or 5% squaric acid on their cold sore within 72 hours of a recurrence. Participants sensitised with placebo solution will receive placebo solution on their cold sore within 72 hours of a recurrence. Participants will be followed for up to 6 months after application of the study medication
Outcomes	1. Primary outcome measures: number of days with lesions 1. Secondary outcome measures: number of days until first participant-reported recurrence and number of adverse events reported
Starting date	October 2013
Contact information	Lynne Hermosilla, Massachusetts General Hospital, Boston, Massachusetts, US, 02114 E-mail: harvardskinstudies@partners.org
Notes	www.clinicaltrials.gov/ct2/show/NCT01971385

CHF: chronic heart failure.
CVA: cerebrovascular accident.
EF: ejection fraction.
HIV: human immunodeficiency virus.
HSV: herpes simplex virus.
IUD: intrauterine device.
MD: Doctor of Medicine.
MI: myocardial infarction.
PI: principal investigator.
SADBE: squaric acid dibutylester.
TIA: transient ischemic attack.
UV: ultraviolet.

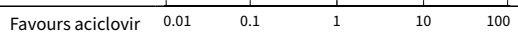
DATA AND ANALYSES

Comparison 1. Oral aciclovir (short-term) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of HSL during use of the preventative intervention (by clinical evaluation)	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Aciclovir 800 mg twice daily	1	237	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.62, 1.87]
1.2 Aciclovir 400 mg twice daily	2	177	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.13, 0.51]
1.3 Aciclovir 200 mg 5 times/day	1	66	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.20, 1.07]
2 Incidence of HSL during use of the preventative intervention (by culture)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Adverse effects during use of the preventative intervention	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Aciclovir 800 mg twice daily	1	239	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.70, 1.38]
3.2 Aciclovir 400 mg twice daily	2	183	Risk Ratio (M-H, Fixed, 95% CI)	2.30 [0.62, 8.58]
4 Severity (lesion size) of attack of herpes labialis during use of the preventative intervention	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Length	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Width	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 Area	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Severity (stage) of attack of recurrent HSL during use of the preventative intervention	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Prodrome	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Erythema	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 Papule	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Severity (pain) of attack of recurrent HSL during use of the preventative intervention	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7 Incidence of HSL after use of the preventative intervention	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

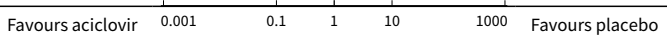
Analysis 1.1. Comparison 1 Oral aciclovir (short-term) versus placebo, Outcome 1 Incidence of HSL during use of the preventative intervention (by clinical evaluation).

Study or subgroup	Aciclovir n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Aciclovir 800 mg twice daily					
Raborn 1998	21/114	21/123		100%	1.08[0.62,1.87]
Subtotal (95% CI)	**114**	**123**		**100%**	**1.08[0.62,1.87]**
Total events: 21 (Aciclovir), 21 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.27(P=0.79)					
1.1.2 Aciclovir 400 mg twice daily					
Schädelin 1988	3/14	13/16		44.93%	0.26[0.09,0.74]
Spruance 1988	5/75	19/72		55.07%	0.25[0.1,0.64]
Subtotal (95% CI)	**89**	**88**		**100%**	**0.26[0.13,0.51]**
Total events: 8 (Aciclovir), 32 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.95); I^2=0%					
Test for overall effect: Z=3.85(P=0)					
1.1.3 Aciclovir 200 mg 5 times/day					
Spruance 1991a	6/33	13/33		100%	0.46[0.2,1.07]
Subtotal (95% CI)	**33**	**33**		**100%**	**0.46[0.2,1.07]**
Total events: 6 (Aciclovir), 13 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.81(P=0.07)					



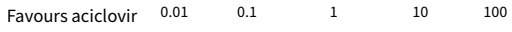
Analysis 1.2. Comparison 1 Oral aciclovir (short-term) versus placebo, Outcome 2 Incidence of HSL during use of the preventative intervention (by culture).

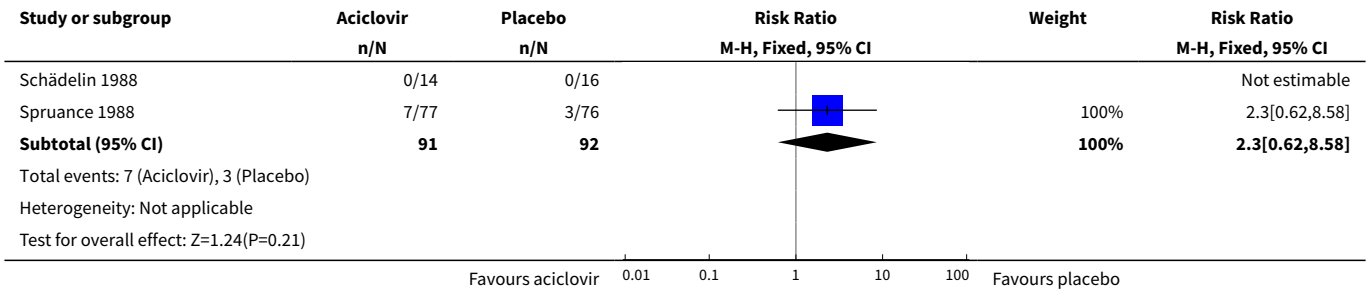
Study or subgroup	Aciclovir n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Schädelin 1988	0/14	12/16		0.05[0,0.7]



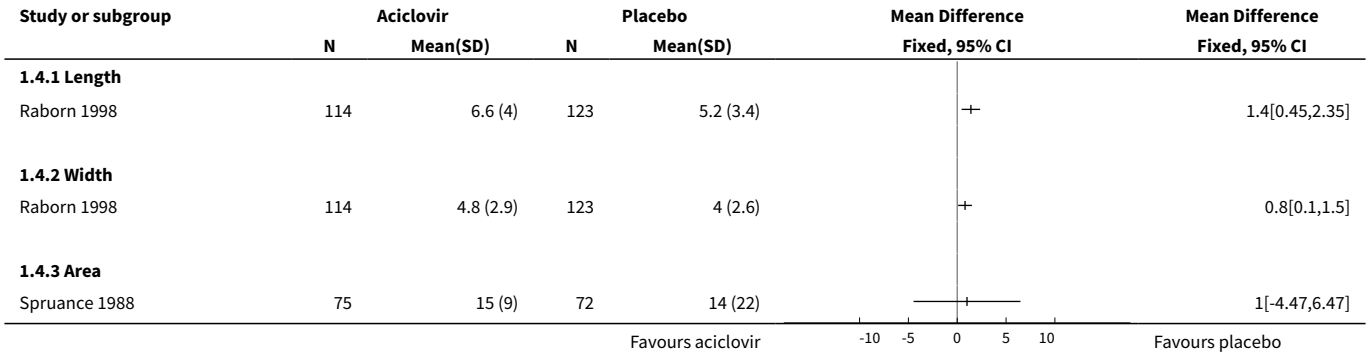
Analysis 1.3. Comparison 1 Oral aciclovir (short-term) versus placebo, Outcome 3 Adverse effects during use of the preventative intervention.

Study or subgroup	Aciclovir n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Aciclovir 800 mg twice daily					
Raborn 1998	41/115	45/124		100%	0.98[0.7,1.38]
Subtotal (95% CI)	**115**	**124**		**100%**	**0.98[0.7,1.38]**
Total events: 41 (Aciclovir), 45 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.1(P=0.92)					
1.3.2 Aciclovir 400 mg twice daily					

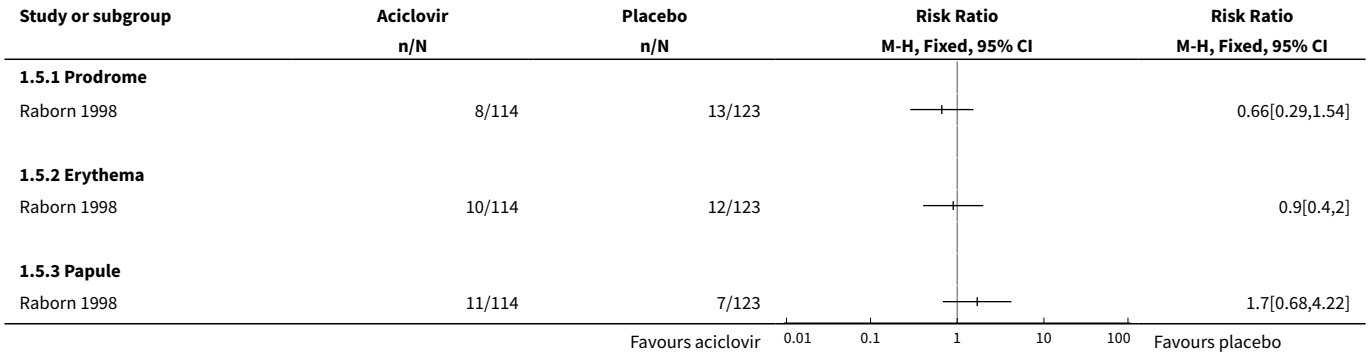




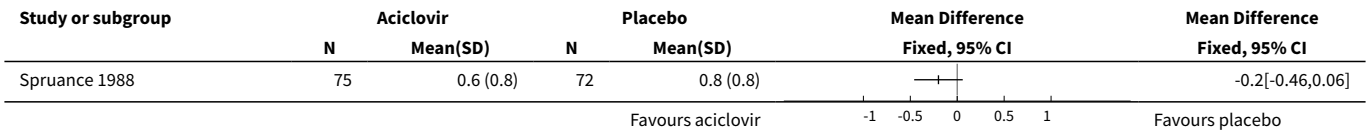
Analysis 1.4. Comparison 1 Oral aciclovir (short-term) versus placebo, Outcome 4 Severity (lesion size) of attack of herpes labialis during use of the preventative intervention.



Analysis 1.5. Comparison 1 Oral aciclovir (short-term) versus placebo, Outcome 5 Severity (stage) of attack of recurrent HSL during use of the preventative intervention.



Analysis 1.6. Comparison 1 Oral aciclovir (short-term) versus placebo, Outcome 6 Severity (pain) of attack of recurrent HSL during use of the preventative intervention.



Analysis 1.7. Comparison 1 Oral aciclovir (short-term) versus placebo, Outcome 7 Incidence of HSL after use of the preventative intervention.

Study or subgroup	Aciclovir n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Spruance 1988	9/75	7/72		1.23[0.49,3.14]

Favours aciclovir 0.01 0.1 1 10 100 Favours placebo

Comparison 2. Oral aciclovir (long-term) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of attack of herpes labialis during use of the preventative intervention	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Oral aciclovir (long-term) versus placebo, Outcome 1 Duration of attack of herpes labialis during use of the preventative intervention.

Study or subgroup	Aciclovir N	Aciclovir Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Rooney 1993	20	4.3 (4)	20	7.9 (7.2)		-3.6[-7.2,-0]

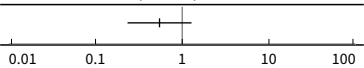
Favours aciclovir -20 -10 0 10 20 Favours placebo

Comparison 3. Valaciclovir (short-term) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of herpes labialis during use of the preventative intervention (by clinical evaluation)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Incidence of herpes labialis during use of the preventative intervention (by culture)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Adverse effects during use of the preventative intervention	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Viral load (shedding) in saliva	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

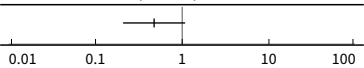
Analysis 3.1. Comparison 3 Valaciclovir (short-term) versus placebo, Outcome 1 Incidence of herpes labialis during use of the preventative intervention (by clinical evaluation).

Study or subgroup	Valaciclovir n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Miller 2004	7/62	13/63		0.55[0.23,1.28]



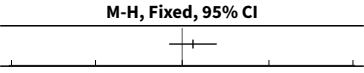
Analysis 3.2. Comparison 3 Valaciclovir (short-term) versus placebo, Outcome 2 Incidence of herpes labialis during use of the preventative intervention (by culture).

Study or subgroup	Valaciclovir n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Miller 2004	7/62	15/63		0.47[0.21,1.08]



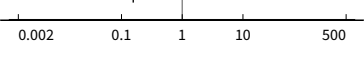
Analysis 3.3. Comparison 3 Valaciclovir (short-term) versus placebo, Outcome 3 Adverse effects during use of the preventative intervention.

Study or subgroup	Valaciclovir n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Miller 2004	17/62	13/63		1.33[0.71,2.5]



Analysis 3.4. Comparison 3 Valaciclovir (short-term) versus placebo, Outcome 4 Viral load (shedding) in saliva.

Study or subgroup	Valaciclovir n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Miller 2004	1/62	6/58		0.16[0.02,1.26]



Comparison 4. Valaciclovir (long-term) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse effects during use of the preventative intervention	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4 Valaciclovir (long-term) versus placebo, Outcome 1 Adverse effects during use of the preventative intervention.

Study or subgroup	Valaciclovir n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Baker 2003	16/47	19/48		0.86[0.51,1.46]

Favours valaciclovir 0.01 0.1 1 10 100 Favours placebo

Comparison 5. Valaciclovir (suppressive regimen versus episodic regimen)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of herpes labialis during use of the preventative intervention (number of recurrences per participant per month)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Adverse effects during use of the preventative intervention	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Duration of attack of recurrent HSL during use of the preventative intervention	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Severity (pain) of attack of recurrent HSL during use of the preventative intervention	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 Severity (maximum total lesion area) of attack of recurrent HSL during use of the preventative intervention	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 5.1. Comparison 5 Valaciclovir (suppressive regimen versus episodic regimen), Outcome 1 Incidence of herpes labialis during use of the preventative intervention (number of recurrences per participant per month).

Study or subgroup	Suppressive regimen N	Suppressive regimen Mean(SD)	Episodic regimen N	Episodic regimen Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Gilbert 2007	60	0.1 (0.1)	60	0.2 (0.2)		-0.1[-0.16,-0.05]

Favours suppressive -0.2 -0.1 0 0.1 0.2 Favours episodic

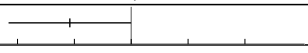
Analysis 5.2. Comparison 5 Valaciclovir (suppressive regimen versus episodic regimen), Outcome 2 Adverse effects during use of the preventative intervention.

Study or subgroup	Suppressive regimen n/N	Episodic regimen n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Gilbert 2007	29/76	24/76		1.21[0.78,1.87]

Favours suppressive 0.01 0.1 1 10 100 Favours episodic

Analysis 5.3. Comparison 5 Valaciclovir (suppressive regimen versus episodic regimen), Outcome 3 Duration of attack of recurrent HSL during use of the preventative intervention.

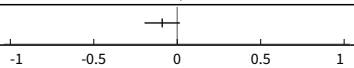
Study or subgroup	Suppressive regimen N	Suppressive regimen Mean(SD)	Episodic regimen N	Episodic regimen Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Gilbert 2007	60	1.8 (2.9)	60	2.9 (3.1)		-1.08[-2.16,-0]



Favours suppressive — Favours episodic

Analysis 5.4. Comparison 5 Valaciclovir (suppressive regimen versus episodic regimen), Outcome 4 Severity (pain) of attack of recurrent HSL during use of the preventative intervention.

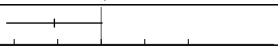
Study or subgroup	Suppressive regimen N	Suppressive regimen Mean(SD)	Episodic regimen N	Episodic regimen Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Gilbert 2007	60	0.1 (0.3)	60	0.2 (0.3)		-0.09[-0.2,0.02]



Favours suppressive — Favours episodic

Analysis 5.5. Comparison 5 Valaciclovir (suppressive regimen versus episodic regimen), Outcome 5 Severity (maximum total lesion area) of attack of recurrent HSL during use of the preventative intervention.

Study or subgroup	Suppressive regimen N	Suppressive regimen Mean(SD)	Episodic regimen N	Episodic regimen Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Gilbert 2007	60	5.1 (10)	60	10.5 (19.5)		-5.38[-10.91,0.15]



Favours suppressive — Favours episodic

Comparison 6. Famciclovir versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of HSL during use of the preventative intervention (by clinical evaluation)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Famciclovir 125 mg	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Famciclovir 250 mg	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Famciclovir 500 mg	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Duration of attack of recurrent HSL during use of the preventative intervention	1		Hazard Ratio (Random, 95% CI)	Totals not selected
2.1 Famciclovir 125 mg	1		Hazard Ratio (Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Famciclovir 250 mg	1		Hazard Ratio (Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Famciclovir 500 mg	1		Hazard Ratio (Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Severity (pain) of attack of recurrent HSL during use of the preventative intervention	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Famciclovir 125 mg	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Famciclovir 250 mg	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Famciclovir 500 mg	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 6.1. Comparison 6 Famciclovir versus placebo, Outcome 1 Incidence of HSL during use of the preventative intervention (by clinical evaluation).

Study or subgroup	Famciclovir n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
6.1.1 Famciclovir 125 mg				
Spruance 1999	23/60	31/60		0.74[0.5,1.11]
6.1.2 Famciclovir 250 mg				
Spruance 1999	22/62	31/60		0.69[0.45,1.04]
6.1.3 Famciclovir 500 mg				
Spruance 1999	26/61	31/60		0.82[0.56,1.21]

Favours famciclovir — Favours placebo

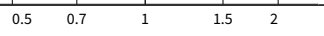
Analysis 6.2. Comparison 6 Famciclovir versus placebo, Outcome 2 Duration of attack of recurrent HSL during use of the preventative intervention.

Study or subgroup	Famciclovir N	Placebo N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI
6.2.1 Famciclovir 125 mg					
Spruance 1999	0	0	0.5 (0.336)		1.63[0.84,3.15]
6.2.2 Famciclovir 250 mg					
Spruance 1999	0	0	0.5 (0.357)		1.59[0.79,3.2]
6.2.3 Famciclovir 500 mg					
Spruance 1999	0	0	0.9 (0.337)		2.39[1.23,4.63]

Favours placebo — Favours famciclovir

Analysis 6.3. Comparison 6 Famciclovir versus placebo, Outcome 3 Severity (pain) of attack of recurrent HSL during use of the preventative intervention.

Study or subgroup	Famciclovir n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
6.3.1 Famciclovir 125 mg				
Spruance 1999	22/23	29/31		1.02[0.9,1.16]
6.3.2 Famciclovir 250 mg				
Spruance 1999	19/22	29/31		0.92[0.76,1.12]
6.3.3 Famciclovir 500 mg				
Spruance 1999	22/26	29/31		0.9[0.75,1.09]



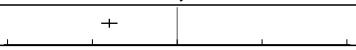
Favours famciclovir — Favours placebo

Comparison 7. Levamisole versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of HSL during use of the preventative intervention	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Adverse effects during use of the preventative intervention (leading to withdrawal)	1		Risk Difference (M-H, Random, 95% CI)	Totals not selected
3 Duration of attack of recurrent HSL during use of the preventative intervention	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 7.1. Comparison 7 Levamisole versus placebo, Outcome 1 Incidence of HSL during use of the preventative intervention.

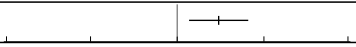
Study or subgroup	Levamisole N	Levamisole Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Russell 1978	29	-2.7 (0.6)	43	-0.7 (0.4)		-2[-2.24,-1.76]



Favours levamisole — Favours placebo

Analysis 7.2. Comparison 7 Levamisole versus placebo, Outcome 2 Adverse effects during use of the preventative intervention (leading to withdrawal).

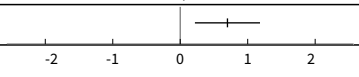
Study or subgroup	Levamisole n/N	Placebo n/N	Risk Difference M-H, Random, 95% CI	Risk Difference M-H, Random, 95% CI
Russell 1978	19/48	8/51		0.24[0.07,0.41]



Favours levamisole — Favours placebo

Analysis 7.3. Comparison 7 Levamisole versus placebo, Outcome 3 Duration of attack of recurrent HSL during use of the preventative intervention.

Study or subgroup	Levamisole		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Russell 1978	29	-0.1 (1.2)	43	-0.8 (0.7)		0.7[0.22,1.18]



Comparison 8. Lysine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of HSL during use of the preventative intervention (number of recurrences per participant per month)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 8.1. Comparison 8 Lysine versus placebo, Outcome 1 Incidence of HSL during use of the preventative intervention (number of recurrences per participant per month).

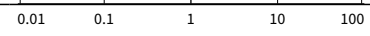
Study or subgroup	Lysine		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Thein 1984	15	0.4 (0.4)	11	0.5 (0.4)		-0.04[-0.37,0.29]

Comparison 9. Topical aciclovir (short-term) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of HSL during use of the preventative intervention	2	271	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.48, 1.72]
2 Adverse effects during use of the preventative intervention	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Severity (aborted lesions) of attack of recurrent HSL during use of the preventative intervention	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Incidence of HSL after use of the preventative intervention	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 9.1. Comparison 9 Topical aciclovir (short-term) versus placebo, Outcome 1 Incidence of HSL during use of the preventative intervention.

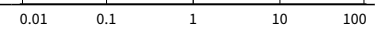
Study or subgroup	Topical aciclovir n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Raborn 1997	15/91	23/90		46.28%	0.65[0.36,1.15]
Spruance 1991c	22/45	18/45		53.72%	1.22[0.77,1.95]
Total (95% CI)	**136**	**135**		**100%**	**0.91[0.48,1.72]**
Total events: 37 (Topical aciclovir), 41 (Placebo)					
Heterogeneity: Tau^2=0.14; Chi^2=2.92, df=1(P=0.09); I^2=65.81%					
Test for overall effect: Z=0.29(P=0.77)					



Favours aciclovir — Favours placebo

Analysis 9.2. Comparison 9 Topical aciclovir (short-term) versus placebo, Outcome 2 Adverse effects during use of the preventative intervention.

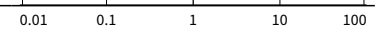
Study or subgroup	Topical aciclovir n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Raborn 1997	15/95	13/96		1.17[0.59,2.32]



Favours aciclovir — Favours placebo

Analysis 9.3. Comparison 9 Topical aciclovir (short-term) versus placebo, Outcome 3 Severity (aborted lesions) of attack of recurrent HSL during use of the preventative intervention.

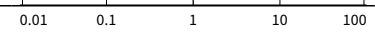
Study or subgroup	Aciclovir n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Spruance 1991c	3/31	2/21		1.02[0.19,5.57]



Favours placebo — Favours aciclovir

Analysis 9.4. Comparison 9 Topical aciclovir (short-term) versus placebo, Outcome 4 Incidence of HSL after use of the preventative intervention.

Study or subgroup	Topical aciclovir n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Raborn 1997	5/91	14/90		0.35[0.13,0.94]



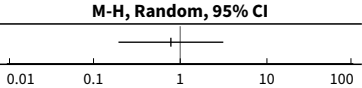
Favours aciclovir — Favours placebo

Comparison 10. Topical aciclovir and 348U87 cream (short-term) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of HSL during use of the preventative intervention (by culture)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Incidence of HSL during use of the preventative intervention (by clinical evaluation)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Duration of attack of recurrent HSL during use of the preventative intervention	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Severity of attack of recurrent HSL during use of the preventative intervention (maximum lesion area)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

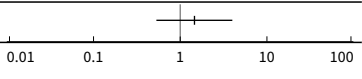
Analysis 10.1. Comparison 10 Topical aciclovir and 348U87 cream (short-term) versus placebo, Outcome 1 Incidence of HSL during use of the preventative intervention (by culture).

Study or subgroup	Aciclovir + 348U87 n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Bernstein 1994	3/25	4/26		0.78[0.19,3.14]



Analysis 10.2. Comparison 10 Topical aciclovir and 348U87 cream (short-term) versus placebo, Outcome 2 Incidence of HSL during use of the preventative intervention (by clinical evaluation).

Study or subgroup	Aciclovir + 348U87 n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Bernstein 1994	7/25	5/26		1.46[0.53,3.99]

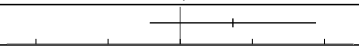


Analysis 10.3. Comparison 10 Topical aciclovir and 348U87 cream (short-term) versus placebo, Outcome 3 Duration of attack of recurrent HSL during use of the preventative intervention.

Study or subgroup	Aciclovir + 348U87 N	Aciclovir + 348U87 Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Bernstein 1994	4	9.3 (3.8)	5	6.8 (1.3)		2.5[-1.39,6.39]

Analysis 10.4. Comparison 10 Topical aciclovir and 348U87 cream (short-term) versus placebo, Outcome 4 Severity of attack of recurrent HSL during use of the preventative intervention (maximum lesion area).

Study or subgroup	Aciclovir + 348U87		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Bernstein 1994	4	143 (112)	5	70 (40)		73[-42.22,188.22]

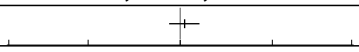


Comparison 11. Topical foscarnet versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of HSL during use of the preventative intervention	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects during use of the preventative intervention (leading to discontinuation)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Adverse effects during use of the preventative intervention (application site reactions)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Duration of attack of recurrent HSL during use of the preventative intervention (healing time)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 Severity of attack of recurrent HSL during use of the preventative intervention (mean lesion area)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Severity of attack of recurrent HSL during use of the preventative intervention (maximum lesion area)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7 Severity of attack of recurrent HSL during use of the preventative intervention (duration of pain)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

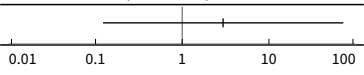
Analysis 11.1. Comparison 11 Topical foscarnet versus placebo, Outcome 1 Incidence of HSL during use of the preventative intervention.

Study or subgroup	Foscarnet	Placebo	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Bernstein 1997	65/148	60/147		1.08[0.82,1.4]



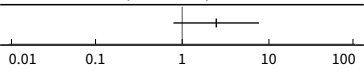
Analysis 11.2. Comparison 11 Topical foscarnet versus placebo, Outcome 2 Adverse effects during use of the preventative intervention (leading to discontinuation).

Study or subgroup	Foscarnet n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Bernstein 1997	1/152	0/150		2.96[0.12,72.11]



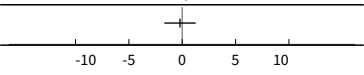
Analysis 11.3. Comparison 11 Topical foscarnet versus placebo, Outcome 3 Adverse effects during use of the preventative intervention (application site reactions).

Study or subgroup	Foscarnet n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Bernstein 1997	10/152	4/150		2.47[0.79,7.69]



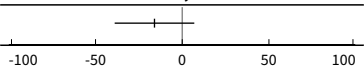
Analysis 11.4. Comparison 11 Topical foscarnet versus placebo, Outcome 4 Duration of attack of recurrent HSL during use of the preventative intervention (healing time).

Study or subgroup	Foscarnet N	Foscarnet Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Bernstein 1997	65	7 (4)	60	7.2 (4.4)		-0.21[-1.68,1.26]



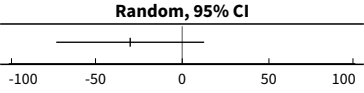
Analysis 11.5. Comparison 11 Topical foscarnet versus placebo, Outcome 5 Severity of attack of recurrent HSL during use of the preventative intervention (mean lesion area).

Study or subgroup	Foscarnet N	Foscarnet Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Bernstein 1997	65	48 (58)	59	64 (71)		-16[-38.96,6.96]



Analysis 11.6. Comparison 11 Topical foscarnet versus placebo, Outcome 6 Severity of attack of recurrent HSL during use of the preventative intervention (maximum lesion area).

Study or subgroup	Foscarnet N	Foscarnet Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Bernstein 1997	65	86 (114)	59	116 (127)		-30[-72.64,12.64]



Analysis 11.7. Comparison 11 Topical foscarnet versus placebo, Outcome 7 Severity of attack of recurrent HSL during use of the preventative intervention (duration of pain).

Study or subgroup	Foscarnet		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Bernstein 1997	61	4.6 (3.9)	52	4.5 (2.6)		0.1[-1.11,1.31]
				Favours foscarnet	-5 -2.5 0 2.5 5	Favours placebo

Comparison 12. Topical 1,5-pentanediol versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Severity (blistering, swelling, or pain) of recurrence	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

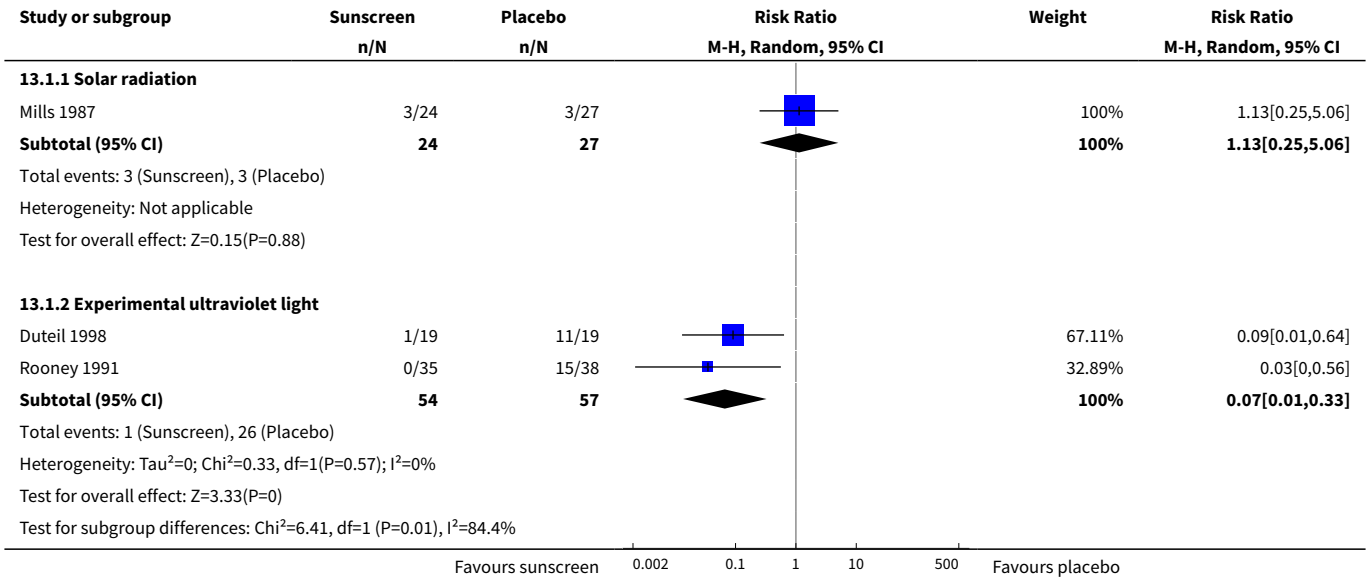
Analysis 12.1. Comparison 12 Topical 1,5-pentanediol versus placebo, Outcome 1 Severity (blistering, swelling, or pain) of recurrence.

Study or subgroup	1,5-pentanediol	Placebo	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Busch 2009	83/105	90/119		1.05[0.91,1.2]
		Favours 1,5-pentanediol	0.5 0.7 1 1.5 2	Favours placebo

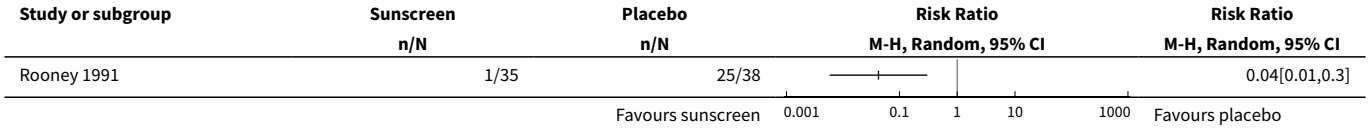
Comparison 13. Sunscreen versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of HSL during use of the preventative intervention (by clinical evaluation)	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Solar radiation	1	51	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.25, 5.06]
1.2 Experimental ultraviolet light	2	111	Risk Ratio (M-H, Random, 95% CI)	0.07 [0.01, 0.33]
2 Incidence of HSL during use of the preventative intervention (by culture)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 13.1. Comparison 13 Sunscreen versus placebo, Outcome 1 Incidence of HSL during use of the preventative intervention (by clinical evaluation).



Analysis 13.2. Comparison 13 Sunscreen versus placebo, Outcome 2 Incidence of HSL during use of the preventative intervention (by culture).

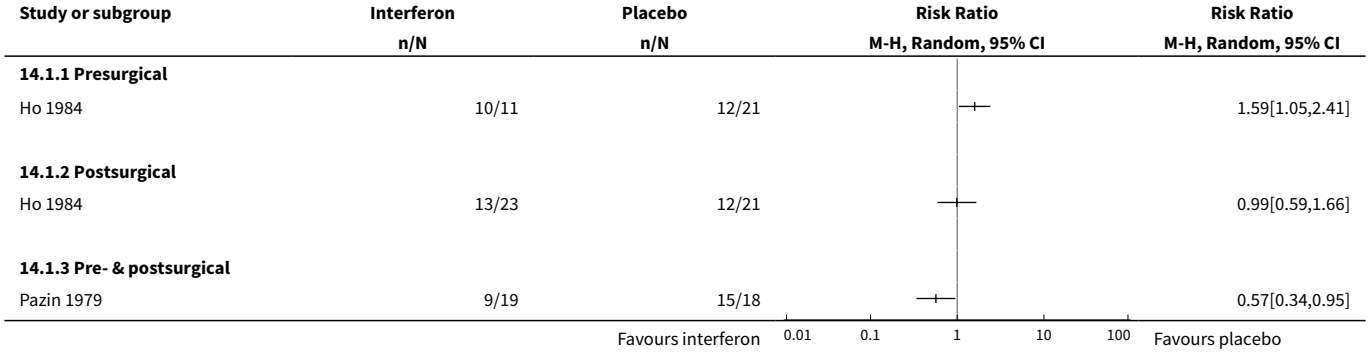


Comparison 14. Interferon versus placebo

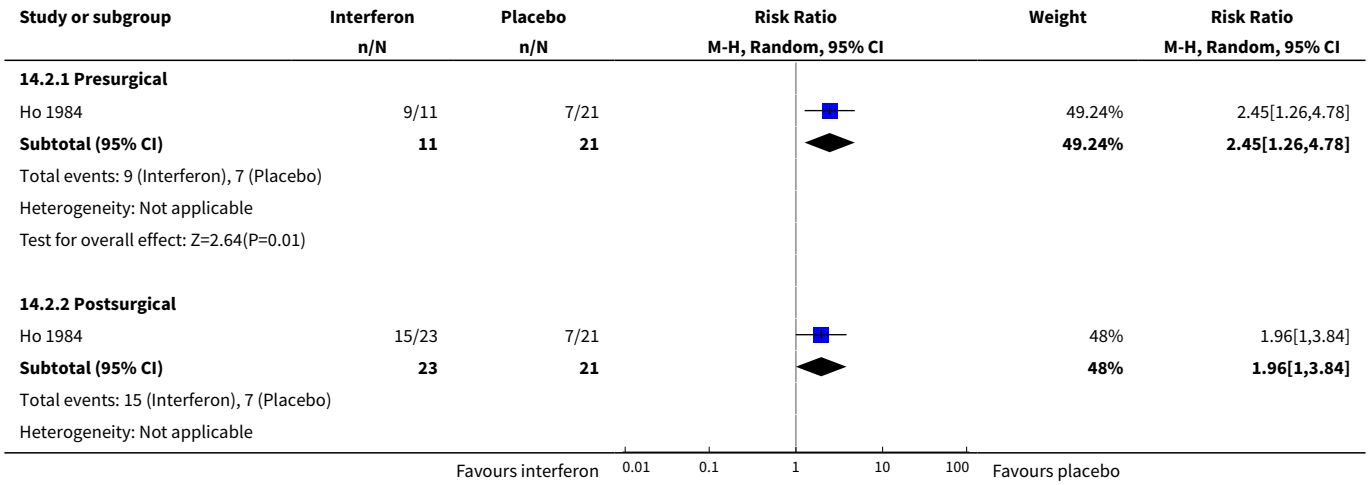
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of HSL during use of the preventative intervention	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Presurgical	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Postsurgical	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Pre- & postsurgical	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Adverse effects during use of the preventative intervention (fever)	2	114	Risk Ratio (M-H, Random, 95% CI)	2.30 [1.44, 3.67]
2.1 Presurgical	1	32	Risk Ratio (M-H, Random, 95% CI)	2.45 [1.26, 4.78]

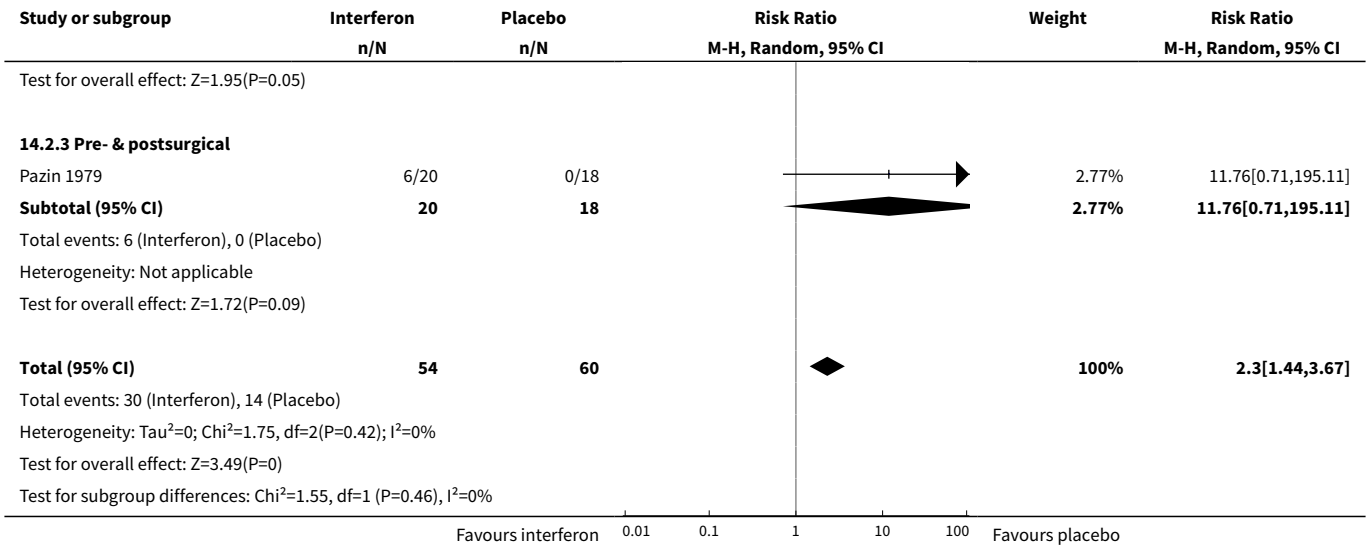
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Postsurgical	1	44	Risk Ratio (M-H, Random, 95% CI)	1.96 [1.00, 3.84]
2.3 Pre- & postsurgical	1	38	Risk Ratio (M-H, Random, 95% CI)	11.76 [0.71, 195.11]
3 Adverse effects during use of the preventative intervention (other)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Pain & tenderness at injection site	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Malaise, nausea or vomiting	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 14.1. Comparison 14 Interferon versus placebo, Outcome 1 Incidence of HSL during use of the preventative intervention.

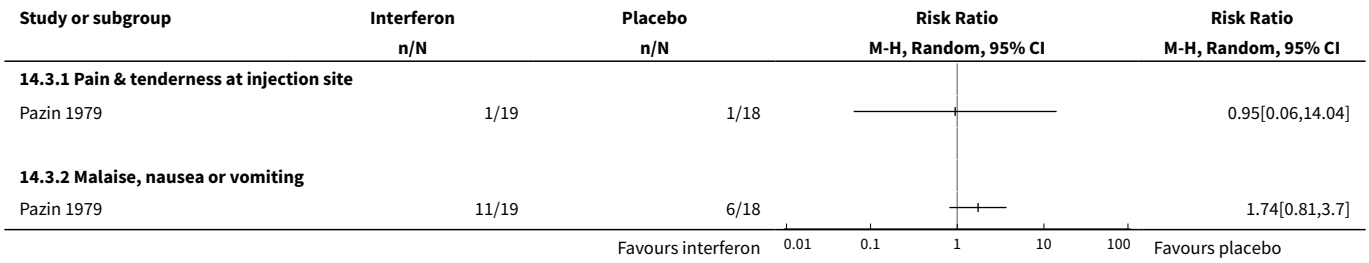


Analysis 14.2. Comparison 14 Interferon versus placebo, Outcome 2 Adverse effects during use of the preventative intervention (fever).





Analysis 14.3. Comparison 14 Interferon versus placebo, Outcome 3 Adverse effects during use of the preventative intervention (other).

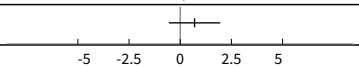


Comparison 15. Gamma globulin versus histamine (control)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of attack of recurrent HSL during use of the preventative intervention	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Severity of attack of recurrent HSL during use of the preventative intervention (less severe recurrences than usual)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

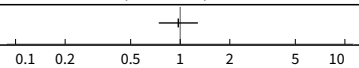
Analysis 15.1. Comparison 15 Gamma globulin versus histamine (control), Outcome 1 Duration of attack of recurrent HSL during use of the preventative intervention.

Study or subgroup	Gamma globulin N	Gamma globulin Mean(SD)	Histamine solution N	Histamine solution Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Redman 1986	35	6.8 (3)	37	6.1 (2.4)		0.7[-0.55,1.95]



Analysis 15.2. Comparison 15 Gamma globulin versus histamine (control), Outcome 2 Severity of attack of recurrent HSL during use of the preventative intervention (less severe recurrences than usual).

Study or subgroup	Gamma globulin n/N	Histamine solution n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Redman 1986	27/37	27/36		0.97[0.74,1.28]

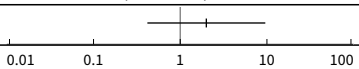


Comparison 16. Thymopentin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse effects during use of the preventative intervention	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 16.1. Comparison 16 Thymopentin versus placebo, Outcome 1 Adverse effects during use of the preventative intervention.

Study or subgroup	Thymopentin n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Bolla 1985	4/18	2/18		2[0.42,9.58]



Comparison 17. Yellow fever vaccination versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse effects during use of the preventative intervention	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 17.1. Comparison 17 Yellow fever vaccination versus placebo, Outcome 1 Adverse effects during use of the preventative intervention.

Study or subgroup	Yellow fever vaccination n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Møller 1997	0/12	1/12		0.33[0.01,7.45]

Favours vaccination 0.01 0.1 1 10 100 Favours placebo

Comparison 18. Laser versus no interventions

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to first recurrence	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 18.1. Comparison 18 Laser versus no interventions, Outcome 1 Time to first recurrence.

Study or subgroup	Laser N	Laser Mean(SD)	No intervention N	No intervention Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Schindl 1999	24	33 (21.3)	24	3 (2.4)		30[21.42,38.58]

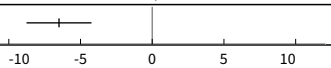
Favours laser -100 -50 0 50 100 Favours no intervention

Comparison 19. Hypnotherapy versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of HSL during use of the preventative intervention (change in frequency of recurrence)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Severity of attack of recurrent HSL during use of the preventative intervention	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 Intensity	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Pain	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Impairment of appearance	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 19.1. Comparison 19 Hypnotherapy versus control, Outcome 1 Incidence of HSL during use of the preventative intervention (change in frequency of recurrence).

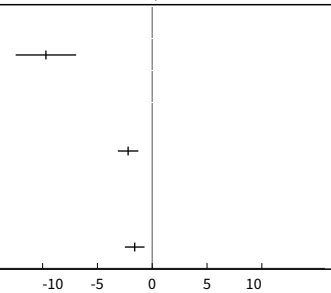
Study or subgroup	Hypnotherapy N	Hypnotherapy Mean(SD)	No hypnotherapy N	No hypnotherapy Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Pfitzer 2005	10	-5.2 (2.6)	11	1.3 (2.7)		-6.5[-8.76,-4.24]



Favours hypnotherapy | Favours no hypnotherapy

Analysis 19.2. Comparison 19 Hypnotherapy versus control, Outcome 2 Severity of attack of recurrent HSL during use of the preventative intervention.

Study or subgroup	Hypnotherapy N	Hypnotherapy Mean(SD)	No hypnotherapy N	No hypnotherapy Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
19.2.1 Intensity						
Pfitzer 2005	10	-11 (3.9)	11	-1.3 (2.2)		-9.7[-12.46,-6.94]
19.2.2 Pain						
Pfitzer 2005	10	-2.1 (1.2)	11	0.1 (1)		-2.2[-3.14,-1.26]
19.2.3 Impairment of appearance						
Pfitzer 2005	10	-2.8 (1.2)	11	-1.2 (0.8)		-1.6[-2.5,-0.7]



Favours hypnotherapy | Favours no hypnotherapy

ADDITIONAL TABLES

Table 1. Trialists contacted for missing or unpublished data

Study	Enquiries	Reply
Baker 2003	We sent the following request on 13 February 2015: (1) How did you randomise the participants? (2) Did you do any measures for allocation concealment? (3) Could you please offer the details of how you achieved double blindness? (4) Did you use a person other than the physician to assess the outcomes?	No reply
de Carvalho 2010	We sent the following request on 23 June 2014: (1) How did you randomise the participants? (2) Did you do any measures for allocation concealment? (3) Did you use a person other than the physician to assess the outcomes? (4) The number of dropouts or withdrawals in this trial (5) Did you assess any outcomes regarding adverse events? If you did, what were the results?	4 August 2014 (1) Randomisation was down through sortition (2) No (3) No (4) 01 (5) Adverse events were evaluated, but there were no

Table 1. Trialists contacted for missing or unpublished data *(Continued)*

		adverse events detected
Gilbert 2007	We sent the following request on 13 February 2015: (1) How did you randomise the participants? (2) Did you do any measures for allocation concealment?	No reply
Pfitzer 2005	We sent the following request on 23 June 2014: (1) How did you randomise the participants? (2) Did you do any measures for allocation concealment? (3) The number of dropouts or withdrawals in this trial (4) Did you assess any outcomes regarding adverse events? If you did, what were the results?	No reply
Senti 2013	This trial was identified from searching trial registers (NCT00914745). We sent the following request on 27 December 2013: "Dear Prof Kündig, I am conducting a Cochrane review on interventions for prevention of herpes simplex labialis (see http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010095/abstract). I have noticed that you have completed a trial (http://clinicaltrials.gov/show/NCT00914745) that assessed a topical ointment for prevention of herpes simplex labialis, and was wondering if you would like to share your results with us, thus we could include your trial in our review. Your assistance would be appreciated"	The trialists provided us with the full published article
ISRCTN03397663	We sent the following request on 27 December 2013: "Dear Dr Cheras, I am conducting a Cochrane review on interventions for prevention of herpes simplex labialis (see http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010095/abstract). I have noticed that you completed a trial that used Sheabutter extract BSP110 for prevention of herpes simplex labialis (http://www.controlled-trials.com/ISRCTN03397663#?close=1). I was wondering if you would like to share your results with us. Thus, we could include your trial in our review. Your assistance would be appreciated"	No reply
NCT01225341	We sent the following request on 27 December 2013: "Dear Dr Dayan, I am conducting a Cochrane review on interventions for prevention of herpes simplex labialis (see http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010095/abstract). I have noticed that you are conducting a trial that uses botulinum toxin A injections for prevention of herpes simplex labialis (http://clinicaltrials.gov/show/NCT01225341). I was wondering if you have completed the trial and would like to share your results with us. Thus, we could include your trial in our review. Your assistance would be appreciated"	No reply
NCT01971385	We sent the following request on 19 January 2014: "Dear Dr Kimball, I am conducting a Cochrane review on interventions for prevention of herpes simplex labialis (see http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010095/abstract). I have noticed that you are doing a trial (http://www.clinicaltrials.gov/ct2/show/NCT01971385) that assessed a topical ointment for prevention of herpes simplex labialis, and was wondering if you would like to share your results with us if you have completed the trial, thus we could include your trial in our review. Your assistance would be greatly appreciated"	No reply

APPENDICES

Appendix 1. Skin & Oral Health Groups' Specialised Registers' search strategy

("cold sore*" or "herpes labialis" or (herpe* and (stomatiti* or gingivostomatiti*)) or "fever blister*") or (("herpes simplex" or herpesvirus or simplexvirus or "hsv-1" or herpes or herpetic or herpesvir* or herpetiform) and (mouth or lip* or labial or orolabial or perioral or extraoral or intraoral or intra-oral or extra-oral or peri-oral or oro-labial or gingiva* or gingivo*))

Appendix 2. CENTRAL (the Cochrane Library) search strategy

#1 MeSH descriptor: [Herpes Labialis] explode all trees
#2 MeSH descriptor: [Stomatitis, Herpetic] explode all trees
#3 "herpes labialis"
#4 (herpe* near/3 (stomatitis or gingivostomatitis*))
#5 "cold sore*" OR "fever blister*"
#6 #1 or #2 or #3 or #4 or #5
#7 MeSH descriptor: [Herpes Simplex] explode all trees
#8 MeSH descriptor: [Herpesvirus 1, Human] explode all trees
#9 MeSH descriptor: [Simplexvirus] explode all trees
#10 "herpes simplex" and simplexvirus and "hsv-1" and herpes or herpetic or herpesvir* or herpetiform*
#11 #7 or #8 or #9 or #10
#12 MeSH descriptor: [Mouth] explode all trees
#13 MeSH descriptor: [Mouth Diseases] explode all trees
#14 MeSH descriptor: [Lip] explode all trees
#15 MeSH descriptor: [Lip Diseases] explode all trees
#16 mouth or lip*1
#17 labial or orolabial or perioral or extraoral or intraoral
#18 "intra-oral" or "extra-oral" or "peri-oral" or "oro-labial"
#19 gingiva* or gingivo*
#20 #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19
#21 #11 and #20
#22 #6 or #21

Appendix 3. MEDLINE (Ovid) search strategy

1. Herpes Labialis.mp. or exp Herpes Labialis/
2. exp Stomatitis, Herpetic/
3. (herpe: adj3 (stomatiti: or gingivostomatiti:)).mp.
4. cold sore$.mp.
5. fever blister$.mp.
6. 1 or 2 or 3 or 4 or 5
7. herpes simplex.mp. or exp Herpes Simplex/
8. exp Herpesvirus 1, Human/
9. simplexvirus.mp. or exp Simplexvirus/
10. "hsv-1".mp.
11. (herpes or herpetic or herpesvir$ or herpetiform$).mp.
12. 7 or 8 or 9 or 10 or 11
13. exp Mouth/ or exp Mouth Diseases/ or mouth.mp.
14. exp Lip/ or exp Lip Diseases/
15. lip$1.mp.
16. (labial or orolabial or perioral or extraoral or intraoral).mp.
17. (intra-oral or extra-oral or peri-oral or oro-labial).mp.
18. (gingiva: or gingivo:).mp.
19. 13 or 14 or 15 or 16 or 17 or 18
20. 12 and 19
21. 6 or 20
22. randomized controlled trial.pt.
23. controlled clinical trial.pt.
24. randomized.ab.
25. placebo.ab.
26. clinical trials as topic.sh.

27. randomly.ab.
28. trial.ti.
29. 22 or 23 or 24 or 25 or 26 or 27 or 28
30. exp animals/ not humans.sh.
31. 29 not 30
32. 21 and 31

Appendix 4. EMBASE (Ovid) search strategy

1. herpes labialis.mp. or exp herpes labialis/
2. exp herpetic stomatitis/
3. (herpe$ adj3 (stomatiti$ or gingivostomatiti$)).mp.
4. cold sore$.mp.
5. fever blister$.mp.
6. 1 or 2 or 3 or 4 or 5
7. herpes simplex.mp. or exp herpes simplex/
8. exp Herpes simplex virus 1/
9. simplexvirus.mp. or exp Simplexvirus/
10. "hsv-1".mp.
11. (herpes or herpetic or herpesvir$ or herpetiform$).mp.
12. 7 or 8 or 9 or 10 or 11
13. exp mouth/ or mouth.mp. or exp mouth disease/
14. exp lip disease/ or exp lip/
15. lip$1.mp.
16. (labial or orolabial or perioral or extraoral or intraoral).mp.
17. (intra-oral or extra-oral or peri-oral or oro-labial).mp.
18. (gingiva$ or gingivo$).mp.
19. 13 or 14 or 15 or 16 or 17 or 18
20. 12 and 19
21. 6 or 20
22. crossover procedure.sh.
23. double-blind procedure.sh.
24. single-blind procedure.sh.
25. (crossover$ or cross over$).tw.
26. placebo$.tw.
27. (doubl$ adj blind$).tw.
28. allocat$.tw.
29. trial.ti.
30. randomized controlled trial.sh.
31. random$.tw.
32. or/22-31
33. exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
34. human/ or normal human/
35. 33 and 34
36. 33 not 35
37. 32 not 36
38. 21 and 37

Appendix 5. LILACS search strategy

(cold sore$) or (fever blister$) or calenturas Or (herpe$ and (stomatiti$ or gingivostomatiti$ or labial$ or simple$ or febril))

Appendix 6. CNKI search strategy

(篇名 = 皰疹) AND (摘要 = 唇) AND (摘要 = 隨機)

Appendix 7. Airiti search strategy

(皰疹) = 篇名關鍵字摘要 AND (唇) = 篇名關鍵字摘要

Appendix 8. Trial register search strategy

herpes labialis

WHAT'S NEW

Date	Event	Description
19 October 2016	Amended	A search of MEDLINE, PubMed, and Embase in October 2016 found only one relevant study of a new intervention, which our Co-ordinating Editor and the lead author decided did not merit an update at this time. Thus, an update of this review has been postponed. Our Information Specialist will run a new search in October 2017 to re-assess whether an update is needed.

CONTRIBUTIONS OF AUTHORS

MC and PK conceived the review.
CC was the contact person with the editorial base.
CC co-ordinated contributions from the co-authors and wrote the final draft of the review.
CC and SW screened papers against eligibility criteria, with FW available for arbitration.
CC obtained data on ongoing and unpublished studies.
CC and SW appraised the quality of papers.
CC and SW extracted data for the review and sought additional information about papers.
CC entered data into RevMan.
CC and SW analysed and interpreted data.
CC worked on the methods sections.
CC drafted the clinical sections of the background and responded to the clinical comments of the referees.
CC responded to the methodology and statistics comments of the referees.
FD was the consumer co-author and checked the review for readability and clarity, as well as ensuring that outcomes were relevant to consumers.
CC is the guarantor of the update.

Disclaimer

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DECLARATIONS OF INTEREST

Ching-Chi Chi: nothing to declare.
Shu-Hui Wang: nothing to declare.
Finola M Delamere: nothing to declare.
Fenella Wojnarowska: nothing to declare.
Mathilde C Peters: nothing to declare.
Preetha P Kanjirath: nothing to declare.

Oliver Chosidow, who refereed this protocol, has acted as a consultant for BioAlliance Pharma, a company developing a long-acting aciclovir formulation in the management of episodic therapy of cold sores.

SOURCES OF SUPPORT

Internal sources

- Chang Gung Memorial Hospital, Chiayi, Taiwan.

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External sources

- The National Institute for Health Research (NIHR), UK.

  The NIHR, UK, is the largest single funder of the Cochrane Skin Group

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We failed to conduct some analyses that we planned in the protocol as follows. Future updates may be different.

1. Because of lacking relevant data, we were unable to implement some methods planned in our protocol, including analysis of time-to-event outcomes and the unit of analysis issue for cluster-randomised trials.
2. We failed to conduct the planned analyses dealing with missing data because of lacking adequate data, for example, the respective number of randomised participants and those who were lost to follow up in each group.
3. We did not assess reporting biases by using a funnel plot because of the limited number of trials for each intervention.
4. We did not perform the planned subgroup analysis and sensitivity analyses because of the lack of relevant data.

The following edits were made in response to comments from the referees.

1. We made some changes to the Background section.
2. We more clearly defined short- and long-term use of interventions.
3. We clarified how our primary outcome of adverse effects and our secondary outcome of adherence was measured and added sentences to the Measures of treatment effect section.
4. In the Unit of analysis issues section, we revised the use of the term 'internally-controlled' and that cross-over and cluster-randomised trials were eligible for inclusion.

We added 'Summary of findings' tables for our primary outcomes for each of our comparisons, which we did not originally plan at the time we wrote our protocol.

NOTES

A search of MEDLINE, PubMed, and Embase in October 2016 found only one relevant study of a new intervention, which our Co-ordinating Editor and the lead author decided did not merit an update at this time. Thus, an update of this review has been postponed. Our Information Specialist will run a new search in October 2017 to re-assess whether an update is needed.

INDEX TERMS

Medical Subject Headings (MeSH)

Antiviral Agents [adverse effects] [*therapeutic use]; Herpes Labialis [*prevention & control]; Randomized Controlled Trials as Topic; Recurrence; Secondary Prevention [methods]

MeSH check words

Humans